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PRECLINICAL AND CLINICAL TESTING BY THE
PHARMACEUTICAL INDUSTRY, 1979

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HEARING

BEFORE THE

SUBCOMMITTEE ON

HEALTH AND SCIENTIFIC RESEARCH

OF THE

COMMITTEE ON

LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

NINETY-SIXTH CONGRESS

FIRST SESSION

ON

EXAMINATION OF THE PROCESS OF DRUG TESTING
AND FDA'S ROLE IN THE PROCESS

OCTOBER 11, 1979



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CONTENTS

CHRONOLOGICAL LIST OF WITNESSES

THURSDAY, OCTOBER 11, 1979

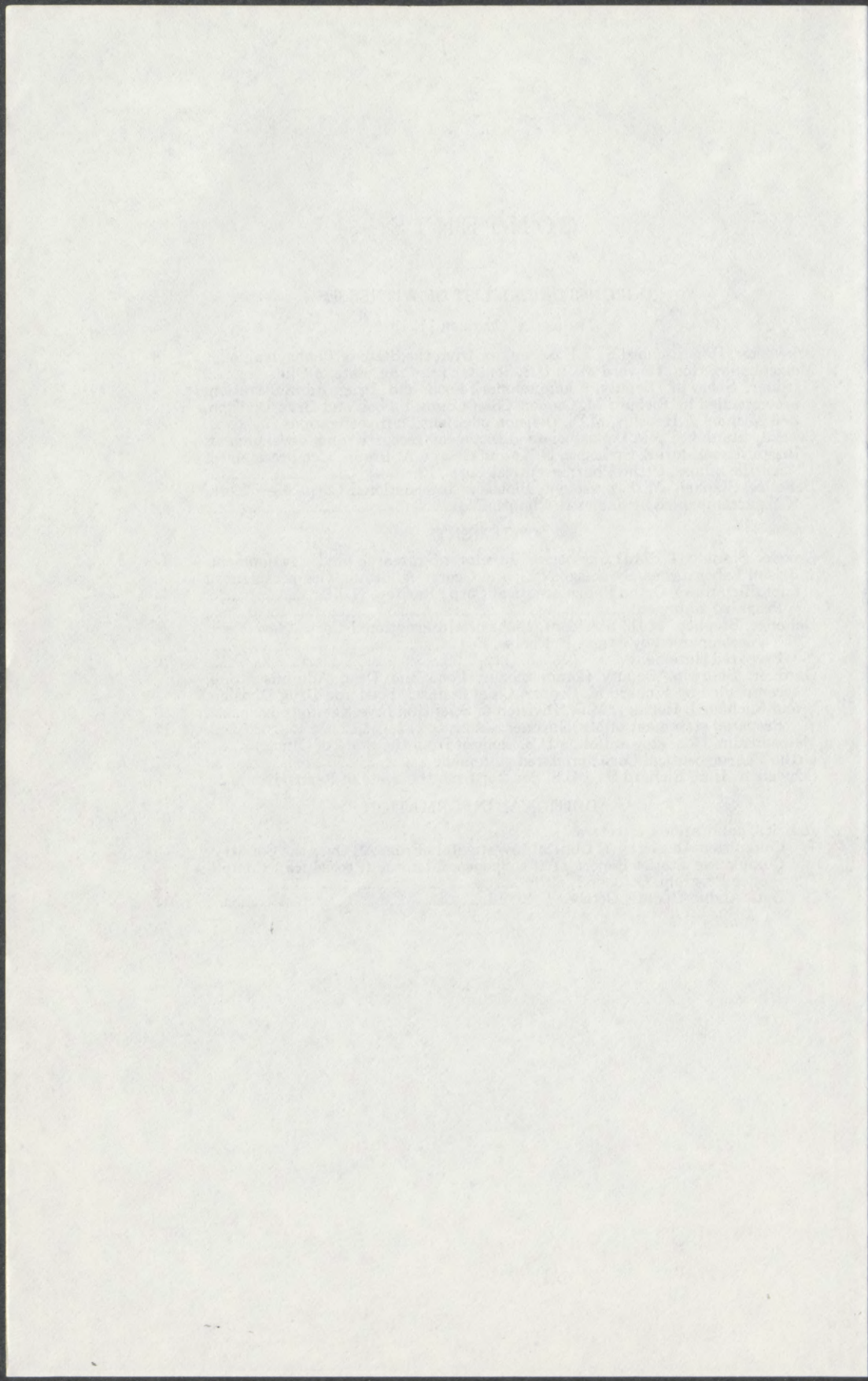
Schweiker, Hon. Richard S., a U.S. Senator from the State of Pennsylvania	Page 8
Metzenbaum, Hon. Howard M., a U.S. Senator from the State of Ohio	9
Gardner, Sherwin, Deputy Commissioner, Food and Drug Administration; accompanied by Richard M. Cooper, Chief Counsel, Food and Drug Division, and Michael J. Hensley, M.D., Division of Scientific Investigations	9
Crooke, Stanley T., M.D., associate director of research and development, Bristol Laboratories, Syracuse, N.Y.; and George A. Braun, vice president of scientific affairs, Ortho Pharmaceutical Corp., Raritan, N.J.	44
DeFelice, Stephen, M.D., president, Biobasics International Corp., New York, N.Y.; accompanied by James R. Phelps, Esq.	62

STATEMENTS

Crooke, Stanley T., M.D., associate director of research and development, Bristol Laboratories, Syracuse, N.Y.; and George A. Braun, vice president of scientific affairs, Ortho Pharmaceutical Corp., Raritan, N.J.	44
Prepared statement	49
DeFelice, Stephen, M.D., president, Biobasics International Corp., New York, N.Y.; accompanied by James R. Phelps, Esq.	62
Prepared statement	70
Gardner, Sherwin, Deputy Commissioner, Food and Drug Administration; accompanied by Richard M. Cooper, Chief Counsel, Food and Drug Division, and Michael J. Hensley, M.D., Division of Scientific Investigations	9
Prepared statement of Mr. Gardner	17
Metzenbaum, Hon. Howard M., a U.S. Senator from the State of Ohio	9
Ortho Pharmaceutical Corp., prepared statement	57
Schweiker, Hon. Richard S., a U.S. Senator from the State of Pennsylvania	8

ADDITIONAL INFORMATION

Articles, publications, et cetera:	
Committed Abuses by 31 Clinical Investigators From All Over the Country .	3
Cumulative Status Report of the Sponsor/Monitor (Procedural) Compli- ance Program, October 1, 1979	12
Data Audits Update, October 1, 1979	11



PRECLINICAL AND CLINICAL TESTING BY THE PHARMACEUTICAL INDUSTRY, 1979

THURSDAY, OCTOBER 11, 1979

U.S. SENATE,
SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9:39 a.m., in room 5110, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittee) presiding.

Present: Senators Kennedy, Metzenbaum, Schweiker, and Hatch.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. We will come to order.

American physicians wrote some 1.5 billion prescriptions in 1977—an average of nearly 7 for every man, woman, and child in America. The American people spend some \$16 billion annually on drug products. And, generally speaking, those dollars purchase the safest, most effective drugs available anywhere in the world. In part, the credit for this goes to the research accomplishments of the pharmaceutical industry; in part, it goes to the Food and Drug Administration, and a regulatory process which prevents potentially dangerous products from reaching the market.

The regulatory process is the barrier to unsafe drugs—it is essential to the protection of the health and safety of the American people. When that process is undermined—as it is when faulty or even fraudulent data is submitted to the FDA and represented as being sound, or when that process is circumvented—as it is when arrogant investigators flagrantly disregard its requirements—then the American people are placed at grave risk.

Today's hearing is about the undermining and circumvention of the regulatory process. It is about serious and, in some instances, unconscionable abuses in human drug testing.

We will hear how 31 clinical investigators, from all over the country, working in various settings—prestigious academic centers, Government facilities, and private practice, committed abuses that include:

1. Altered or falsified laboratory work.
2. Significant, unreported protocol violations.
3. Inadequate proof that the study was actually ever done.
4. Falsified patient consent forms and misrepresentation of how consent was obtained.
5. Falsified or misleading evidence of Institutional Review Committee approval.

6. Completely false patient study records.
7. Failure to report concomitant treatments which would negate the study.
8. Misrepresentation of medical histories.
9. Substantial delay in or refusal of access to records, and
10. Flagrant disregard of FDA rules, including testing drugs in human subjects in spite of specific direction not to test them in humans.

I am releasing a summary chart detailing the violations. Because some of these investigators may be subject to criminal penalties, no clinical investigator will be identified by name—only by number and type of abuses.

[The summary chart referred to follows:]

	Failure to Report Interfering Medication Given at Same Time as Study Medication	Misrepresentation of Medical History	Altered or Falsified Lab Work	Significant Unreported Protocol Violations	Inadequate Documentation to Show Test Drug Ever Given	Falsified Patient Consent Forms, Inadequate Consent or Misrepresentation of How Consent Obtained	Falsified or Misleading Evidence of Institutional Review Comm. Approval or Failure to Obtain IRC Approval	Patients Never Actually Entered Study (Records Completely False)	Substantial Delay in or Refusal of Access to Records
Irvine, CA			X						
Boston		X	X		X				
Indianapolis	X	X	X	X		X			
Los Angeles	X	X		X	X	X		X	
Los Angeles		X	X		X			X	
Washington, DC - Georgetown U.		X			X				X
Washington, DC - Georgetown U.		X	X		X				
New York City - Columbia U.	X	X					X		
Long Beach, CA		X	X	X	X	X	X		X
Phoenix, AZ	X	X	X	X				X	X
Providence, RI		X	X						X
Lansing, MI		X							X
Alexandria, VA					X		X		X
Humacao, PR	X	X	X		X	X		X	X
Los Angeles	X	X	X	X	X	X	X	X	X
Bethesda, MD	X	X		X	X		X		
New Orleans		X		X	X				
Boston	X	X	X	X					
Englewood, NJ									X
Birmingham, AL	X	X	X	X			X		
New York City			X		X				X
Minneapolis	X	X		X		X			X
Philadelphia, PA	X	X		X	X	X		X	X
Abington, PA	X	X	X	X	X				X
Los Angeles		X				X			
Washington, DC					X			X	X
Salt Lake City	X				X		X		X
Fairfax, VA								X	X
Miami		X		X					X
Los Angeles		X		X		X	X		X

Investigation #16 Representative Observations

Subject Identification	Case Report Says	Patient Chart says
AA	Hypertension never present	History of hypertension
	Urinalysis reveals no albumin, no casts	Urinalysis reveals 3 (+) protein, occasional casts
	4 chest x-rays all indicate enlarged heart and poor function	4 chest x-rays normal for age and sex.
WJ	Gastrointestinal problems never present	Chronic esophageal problem
	Angina once present, now inactive	Active angina
	Concomitant treatment limited to Lasix & Digoxin	Concomitant treatment Clonidine, Lasix, Valium, Tylenol, Klorvess
JS	Hypertension, diabetes and pulmonary emboli never present	Patient hypertensive, insulin dependent diabetic, and has had two pulmonary emboli
RU	No history of alcoholism, drug abuse, hypertension, diabetes or lupus erythematosus	Alcoholic with history of drug abuse, hypertension, insulin dependent diabetes, and drug induced lupus erythematosus
	History of myocardial infarction, "now inactive"	Cardiac scan shows possible acute myocardial infarction
	Concomitant treatments were digoxin, hydrochlorothiazide, and potassium chloride	Concomitant treatments were Norpace, insulin, colace, Kloress hydrochlorothiazide
	Chest X-rays taken 11/28/77, 12/12/77, 1/2/78, & 1/23/78	Chest X-rays taken 11/2/77, 11/4/77, 11/21/77 & 1/17/78
	Chest X-ray shows enlarged heart and poor cardiac function.	Chest X-ray shows heart size normal
BJ	No history of past or present liver disease or heavy alcohol intake	Enlarged liver discovered during second study week (4/15/75). History of moderate to heavy alcohol intake
	Lab work 4/15/75	Lab work 4/15/75
	a) S G O T 27	a) S G O T 375
	b) alkaline phos. 45	b) alkaline phos. 177
	c) bilirubin 0.7	c) bilirubin 3.0
	Lab work 5/20/75	Lab Work 5/20/75
	a) S G O T 30	a) S G O T 72
	b) alkaline phos. 48	b) alkaline phos. 133
	c) bilirubin 0.7	c) bilirubin 1.7

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Typical observations. Inspection of Investigation #12

(A) Study #1

Subject Number	Case Report Form	Patient Chart
11.	Study drug given at 9:00 A.M. on 8/11/78, the patient having had Tylenol at 3:00 A.M. on 8/11/78. No other pain relievers given, until patient required additional Tylenol later in the day.	Study Drug never given. Patient had Tylenol at 3:45 A.M. 8/11/78, and received aspirin at 10:00 A.M. on 8/11/78. Did not subsequently receive Tylenol.
	Only one concomitant medication listed.	Several concomitant medications listed.
	No history of alcoholism noted.	Patient is an alcoholic with a history of D.T.'s.
18.	Patient has surgery on 8/15/78, receives study drug at 9:00 A.M. on 8/16/78.	Patient has surgery 8/18/78, and there is no record of the investigational drug ever being given.
	Morphine listed as preoperative medication, and Rheomacrodex listed as concomitant medication.	Patient never received morphine or Rheomacrodex.
20.	Patient had surgery on 8/15/78, got study drug at 8:25 A.M. on 8/18/78, and was re-medicated with Tylenol at 10:25 A.M., 8/18/78.	Surgery actually 8/16/78, and there is no mention of the study drug. Did get Tylenol at 12:00 A.M. on 8/18/78.
45.	Patient had surgery 9/22/78 and study medication at 1:00 P.M. on 9/27/78.	Patient admitted 9/25/78, did not have surgery, did not receive study drug, and was discharged prior to time of alleged study on 9/27/78.
58.	Patient had surgery 10/2/78, and was given study drug at 5:30 P.M. 10/5/78, with observation of effect until 10:20 P.M.	Patient not admitted until 10/3/78 never received study drug, and was discharged at 5:30 P.M. on 10/5/78.

(B) Study #2

Subject Number	Case Report Form	Patient Chart
10052	Surgery 11/10/78, with study drug given at 10:30 A.M. 11/13/78. Patient treated with Tylenol on 11/13/78, at 0600 and 1430.	Surgery actually on 11/14/78, and study drug never given. Tylenol given at 1300, 11/13/78.
10055	Surgery on 11/13/78, with study drug given at 12:00 A.M. on 11/16/78.	Patient's jaws wired shut, unable to take capsules. Discharged on 11/15/78, never given study drug.
10062	Surgery on 11/18/78, with study medication 11/20/78 at 10:00 A.M.	Surgery actually done 11/24/78. Never received study medication. Received demerol at 10:30 A.M., 11/20/78, not noted in case report.
10104	Surgery 12/30/78, given study drug 1/2/78.	Surgery actually 12/20/78, and patient discharged 12/23/78. Never received study drug.

Senator KENNEDY. Some of what we will hear today is both shocking and indefensible. Some of it represents just plain sloppiness. Virtually all of it went undetected for significant periods of time by the pharmaceutical companies and independent contractors involved. Much of it ought to be, and can be, prevented.

The practice of medicine involves a sacred trust. A physician testing drugs for the first time on human subjects has an obligation not only to the test subject—but to the thousands of people who may some day take the drug in part because of the results of that study.

I believe the vast majority of American physicians earn that special trust every day. I believe the majority of clinical investigators meet their extraordinary responsibilities. But some of the abuses we will hear about today are so profound, so indefensible, and so potentially dangerous that the number of them is less important than the fact they exist at all when they do not have to. Better selection of clinical investigators, better monitoring, more careful in-progress reviews by the sponsoring companies can eliminate the bulk of these problems.

That monitoring has clearly been deficient up to now. As a result, we do not know the full extent of the information. There are 2,000 active clinical investigators in the United States in any given year, and they conduct some 12,000 studies. If only 10 percent of the data is faulty and not detected, the problem is enormous.

The Food and Drug Administration has been struggling to finalize clinical investigation regulations for over 2 years. They can have a major impact on solving this problem. We will explore some of those proposed regulations today to see if they are adequate. And this committee will do all it can to see that they are promulgated in final form as soon as possible. Until they are, until cur-

rent monitoring practices improve, the American people will be at unacceptable risk.

Senator Schweiker.

**STATEMENT OF HON. RICHARD S. SCHWEIKER, A U.S. SENATOR
FROM THE STATE OF PENNSYLVANIA**

Senator SCHWEIKER. Thank you, Mr. Chairman.

In the United States, doctors write about 1.5 billion prescriptions for their patients each year. American consumers believe, and have a right to expect, that these products are proven, safe, and effective therapies. It is the Food and Drug Administration's business to guarantee it, through the drug approval system. It is the responsibility of the pharmaceutical industry and those who conduct drug testing to insure that reliable data demonstrating safety and effectiveness are submitted to FDA when they seek to market drugs in the United States.

The integrity of the whole system of drug regulation and approval in this country rests upon the quality of the data developed in support of new drug applications submitted to FDA. If the data is deficient, the whole system has failed. Unfortunately, in a continuing series of hearings over the years, our Health Subcommittee has found that in too many cases, the data upon which FDA is supposed to make its decisions is woefully deficient. Witnesses have described how data have been fabricated for studies reported to FDA which were never done.

We have heard about patients who supposedly benefitted from the drug being tested, who, in fact, never received the drug at all, or who never had the disease being studied, or who were receiving several medications at the same time.

Codes have been broken in supposedly double-blind studies, possibly influencing the interpretation of the studies' outcome. We have found abuses of the rights of human subjects of research and failure to secure any semblance of appropriate and voluntary informed consent.

These kinds of abuses make a mockery of our Nation's drug laws and pose serious, substantial risks to patients and the public health. They cannot be tolerated.

As the ranking Republican on this subcommittee, I am concerned about the persistence of reports of allegedly false, fraudulent, or otherwise deficient, drug test data. Fortunately, many of the drugs in question never make it to the market, because the problems are detected by the FDA or the drug company supporting the testing. Today, our hearing focuses on new instances of allegedly faulty data submitted to FDA.

Food and Drug Administration officials will testify how these problems came to their attention, and how the FDA's system of data review is designed to protect against the acceptance of poor data as a basis for drug approvals. I also expect spokesmen from affected firms to describe the measures they are taking to insure insofar as possible that the data developed in support of their products are reliable and accurate.

Isolated instances of abuse are unlikely to ever be completely eliminated. In this imperfect world, it is probably impossible to design a system that will provide absolute protection as long as

there are investigators who are determined to thwart it and cheat on the data. But we must endeavor to make certain that our monitoring system is sensitive enough to detect problems and strong enough to deter future abuses, so that the American people can rely with confidence on the drugs prescribed for them. Anything less is a betrayal of public trust.

Thank you, Mr. Chairman.

Senator KENNEDY. Senator Metzenbaum.

**STATEMENT OF HON. HOWARD M. METZENBAUM, A U.S.
SENATOR FROM THE STATE OF OHIO**

Senator METZENBAUM. Mr. Chairman, I am deeply disturbed about the topic of today's hearings. We are not talking today about drug industry profits or about the merits of Federal regulation or about the best means to encourage new research. Today, Mr. Chairman, the subcommittee will hear testimony on the use of falsified research results to justify the marketing of drugs to the people of this country.

I commend you, Mr. Chairman, for bringing this problem to light, and for those who have dug up the necessary information in order for it to make it possible for us to go forward. I share with you a determination to find out how this happened and why it happened and to find ways to prevent such abuses in the future.

I know that in many cases the drug companies were not aware of the misleading information being provided to them, but I believe, and I am sure the industry agrees, that drug manufacturers have a moral and legal obligation to be sure that this data is valid and fully reliable. The public, Mr. Chairman, should have the right to take that for granted. I hope that today's witnesses will be able to provide this subcommittee with suggestions on how fraud and abuse in the drug testing process might better be detected in the future.

Thank you, Mr. Chairman.

Senator KENNEDY. Very fine.

Thank you very much, Senator Schweiker and Senator Metzenbaum. We look forward to our first panel this morning.

We have Acting Commissioner Gardner from FDA, accompanied by Richard Cooper, General Counsel, FDA, and Michael Hensley, medical officer in the FDA Office of Scientific Investigations.

We welcome you and ask you to proceed in your own way, Mr. Gardner.

**STATEMENT OF SHERWIN GARDNER, DEPUTY COMMISSIONER,
FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY RICHARD M. COOPER, CHIEF COUNSEL, FOOD AND DRUG DIVISION, AND MICHAEL J. HENSLEY, M.D., DIVISION OF SCIENTIFIC INVESTIGATIONS**

Mr. GARDNER. Thank you, Mr. Chairman.

When we last appeared before this subcommittee to discuss the bioresearch monitoring program in March of 1978, we reported some early results from compliance activities that were undertaken with funds approved in 1976 in order to assure the quality and validity of research submitted to the Food and Drug Administra-

tion. We discussed several case histories of human drug trials that involved both deviations from good scientific practice and disturbing violations of the rights of human subjects involved.

Because the subcommittee has indicated a special interest in clinical investigations of human drugs and in the monitoring of those studies by drug firms and other sponsors, I would like to concentrate on these areas of our program in my testimony today.

Since the time we last testified on this subject, we have gained added insight into the scope of the problem, as a result of over 200 procedural or "data audit" investigations of physicians and through over 100 associated inspections of most of the pharmaceutical manufacturers sponsoring and monitoring their work. I am providing for the record an analysis of the findings of these investigations prepared by our Bureau of Drugs. That Bureau also conducts an extensive program of "for cause" inspections of clinical investigators and monitors of investigational drug studies.

Both the data audit and the "for cause" audit evaluate records underlying data submitted to FDA, but one is of a general surveillance nature while the other involves more intensive inspectional work. "For cause" inspections are generally carried out when there is reason to believe that the work of a clinical investigator is faulty or unreliable. Data audit inspections, on the other hand, are undertaken even when problems are not suspected. They are designed primarily to educate and evaluate researchers by making them aware of the most common procedural deficiencies. These audits provide FDA with a broad picture of the quality of drug evaluation in this country. They also give us insight into the types of serious deficiencies that might be probed in greater detail in "for cause" inspections. Finally, the data audit program audits research being performed in support of important new drug applications pending approval at FDA.

The two programs—"for cause" and data audit—are, in our view, closely interrelated and equally important tools for evaluating and bringing about necessary corrections in human drug testing. Our most recent experience with both programs closely parallels our earlier findings. On the one hand, although we have found a high percentage of procedural deficiencies, the great bulk of the research being conducted is of acceptable quality, and human test subjects are receiving adequate protection. On the other hand, we are still finding a number of investigators whose work represents sloppy science, disregard for the rights of test subjects, and misrepresentation of test data.

We are taking steps, including disqualification of clinical investigators and recommendations of criminal action to the U.S. Attorney, in all cases where such action is warranted. Since we last testified before this subcommittee, we have disqualified 11 clinical investigators, bringing the total number ineligible to receive investigational drugs to 33. We are currently working on the cases of 29 physicians whose deficiencies are such that disqualification and/or clinical prosecution appears warranted. Only two of these were discussed here in March 1978. A tabular summary of the significant problems found in these investigations will be provided for the record.

[Information supplied for the record follows:]

DATA AUDITS UPDATE - 10/1/79

From June 1977 to October 1, 1979, 266 clinical investigator (Data Audit) inspections have been issued by the Bureau of Drugs, Division of Scientific Investigations. 259 have been received by the Bureau to date. Of these:

Washouts	41
Cancellations	5
Not evaluable	1
In review process	7
Evaluable	205

Number of Data Audits requiring response from clinical investigators. (All have been received)	4
--	---

Number of investigators with no meaningful deficiencies whatsoever	42	20% (% of 205)
--	----	----------------

Number of For Cause Investigations developed from Data Audit inspections	18	9%
--	----	----

Most Common Deficiencies

Problems with documentation or completeness of patient consent	73	35%
Inadequate drug accountability	64	31%
Protocol adherence	38	20%
Records accuracy	36	17%
Records availability	13	6%

Other Deficiencies Found

Concomitant therapy	7	3.4%
Inappropriate payment to volunteers	4	1.9%
Use of drug before IND submission	3	1.5%
Inappropriate use/commercialization of IND	2	1.0%
Inadequate follow up of adverse reactions	2	1.0%
Failure to list additional investigators on 1572 or 1573	2	1.0%
Inappropriate patient selection	2	1.0%
Inappropriate delegation of authority	2	1.0%
Patients receiving simultaneous investigational new drugs	1	0.5%
Treatment with outdated drug	1	0.5%

Average number of days from inspection until receipt of inspection report 28

Average number of days to complete reviews (this month) 9.4

Average number of days to complete reviews (this year) 12.2

CUMULATIVE STATUS REPORT OF THE SPONSOR/MONITOR (PROCEDURAL)
COMPLIANCE PROGRAM - 10/1/79

This program involves inspection against proposed regulations of 9/27/79. From 6/77 through 10/1/79, 134 Sponsor/Monitor inspections have been issued by the Bureau of Drugs, Division of Scientific Investigations. Of the 134 that have been received:

Washouts	17
Cancellations	3
Not evaluable	7
In review process	0
Evaluable	107

	<u>Number</u>	<u>% of 107</u>
Sponsors with whom no significant deviations from current or proposed regulations were noted	52	48.6
Sponsors with whom significant deviations were noted	55	51.4
Some of the more frequent deficiencies noted are:		
Failure to establish adequacy of laboratory facilities used by clinical investigator	29	27
Failure to maintain adequate records of drug accountability	29	27
Absence of standard monitoring procedures	28	26
Failure to review patient records	25	23
Failure to assure IRB approval	20	19
Failure to document monitoring visits	17	16
Failure to visit study site before and during clinical study	11	10
Number of sponsors who have definitely indicated that they have compared clinical records with case reports	36	34
Number of sponsors who have a definite policy not to inspect patient records	25	23
Average number of days from date of inspection until receipt by HFD-180 (those received this month)	16	
Average number of days to complete review (this month)	6	

Senator KENNEDY. As I understand, since our last hearing, an additional 27 have been found and investigated, is that correct, since our last set of hearings?

Mr. GARDNER. Since our last hearing, yes, Senator, that is correct.

Senator KENNEDY. OK. Please proceed.

Mr. GARDNER. Our recent experience only reinforces the earlier findings that some significant deficiencies still exist in the testing of investigational drugs. Regretfully, these problems apply not only to physicians who conduct investigations in their private offices, but also to those doing research in academia and under Government sponsorship.

Senator KENNEDY. That is a rather significant factor, that it just is not in a particular type of setting where these investigations which have been followed up on by the FDA have occurred. They have occurred at some of our finest academic universities and in some of the most prominent research centers in the country, and I think that this is important to understand as we are moving on through the course of this hearing. Let us proceed.

Mr. GARDNER. Without identifying the individuals involved, since these cases are still pending, we are prepared to discuss here today with the subcommittee some details of our findings in these investigations.

It is evident that FDA cannot oversee all of the drug trials conducted under our authority, nor would we argue, should we. The legislative history of the Federal Food, Drug, and Cosmetic Act makes it clear that the Congress wanted that responsibility to rest with the sponsor of the study, which, in most instances, is a drug company. Whereas the responsibilities of sponsors have been defined to some extent in current regulations, these regulations are no longer adequate to cope with present-day problems.

Recognizing this, we proposed regulations setting forth the obligations of sponsors and monitors in September 1977. At the same time, FDA began inspections using the proposed regulations as a standard, both to measure the performance of sponsors and monitors and to assess the merits of the proposed regulations.

The final regulations will require monitoring not only of investigational new drug studies but also investigational studies of medical devices, biologicals, and food additives. They will require personal visits by the monitor to the investigator and encourage the monitor to review source documents to assess the validity of the reports to be submitted to the FDA.

Senator KENNEDY. This is really the point of our hearings. Should companies not be required to just not encourage, but required to check the raw data? Otherwise, I do not see how you are going to ever have assurance that those deficiencies are not going to continue to exist.

Mr. GARDNER. That was our thinking when we proposed the regulations, Senator. Some of our experience since making that proposal has caused us to reassess that. I think it is a tough question, and one of the problems we are faced with is that of providing a double standard, if I could elaborate on that for just a moment.

In some of the recent congressional testimony on the assumed drug lag, and on new drug legislation, there has been an interest in making available for evaluation and approval of new drugs here more work that has been done overseas. Now, we have found that it is virtually impossible to get access to the patient's records in overseas clinical investigation settings. Government representatives of the regulatory authorities of those countries, have told us that it is simply not permissible under their laws. So a double standard would come about if we were to require this. Review of patient's records would be a requirement only on drug companies whose investigators are doing work in this country but not abroad, since it could not be enforced there.

So, if we were to insist on that as a requirement, that is where the double standard would arise.

Senator KENNEDY. The American people are going to be held hostage to what the standards are in other countries. I mean they are already being held hostage with regard to oil set in the Middle East, at a very serious disadvantage to the consumers in this country. You have your own Chief of Clinical Investigators Branch saying that monitoring regulations are worthless if this provision is substantially modified and that access by the monitor to subject records is essential to the concept of monitoring. I view this as the single most important point in the entire regulatory system relative to clinical investigations.

Here is the man who has got the principal responsibility to protect the American consumer saying that this is absolutely vital. You are here suggesting that because either the British or the French or some other foreign country is not going to permit the access to that information, then we are not going to provide the best kind of protection to the American consumer that we can.

Mr. GARDNER. Well, I have not come down on that in concrete, Senator. I am simply pointing out what some of the problems are.

Senator KENNEDY. Well, it seems to me that, given the range of abuses that we are going to have in the course of your investigations, such as we are going to hear about today, it just seems to me that your new proposed regulations are inadequate. Two years ago, those proposed regulations provided for periodic visits which would include review of source documents and case reports for adequacy of entries of data.

Your own recommendations 2 years ago suggested that.

Someone must have thought that it was a good idea when you made the recommendations. It just seems to me what we have seen is a retreat from that position at a time when you are finding out very dramatic and serious abuses, in the falsification and sloppy work, and sometimes in the fraudulent misrepresentation of scientific data relative to the testing of prescription drugs, which are absolutely essential to the well-being and the good health of the American people.

Mr. GARDNER. Well, I certainly agree that access to the patient records is important, and as long as we have and continue to have access to patient records, there is a way to get at that.

One of the other problems, Senator, is if we are to enforce that sort of requirement on drug companies, that would very likely have the effect of driving research overseas. If drug companies found

that that sort of requirement was too onerous to conduct research in this country, then that research would then be driven overseas. That is a consideration.

Senator KENNEDY. Are you saying that the access to data to protect the American consumer is going to move that whole industry overseas; is that what you are saying? We are not going to be able to protect the American consumer by being able to get access to raw data; is that what you are suggesting?

Mr. GARDNER. I am suggesting that that might be a consequence of that sort of requirement. If the FDA can get access to records, it may not be necessary to impose that as a requirement on drug companies.

Senator KENNEDY. Well, we are going to hear from one of the drug companies that would differ with your own position on that, and that they believe that it should be available, and there is nothing suggesting that they are thinking about moving overseas.

What we are basically talking about is—given the range of abuses that we have seen and that we will see today—is giving to the FDA, whose responsibility it is to provide for the safety and the efficacy of drugs, the assurances of the scientific quality of testing data. We will have testimony from drug company officials who think that they should have that information. Your own people who have responsibility within the agency think that is the only way that you can really be assured of providing proof of safety to the consumers.

It just seems to me that that certainly ought to be the recommendation.

Well, let us proceed.

Mr. GARDNER. The proposed regulations covering sponsors and monitors will also require that the records be made of these visits and that these records be available for review by the FDA. Finally, they will provide for the possible disqualification of a sponsor or his agents for serious violations of the monitoring regulations.

Through these regulations we hope to achieve better direct monitoring and evaluations by drug firms. We are not, however, turning over the entire job of investigator oversight to the sponsor. Our Bioresearch Monitoring inspection programs are ongoing, and we will continue to conduct on-site investigations of key studies important to the approval of the new drug application submitted to us. The proposed sponsor/monitor regulations are scheduled to be published in final form by the end of the year.

Possibly as a direct result of our investigative activities and your subcommittee's continuing interest in exposing poor research practices, drug company sponsors have been employing to an increasing extent outside contractors to monitor clinical investigators. This arrangement cannot relieve the drug company from its legal responsibility to monitor the investigation, and it creates yet another layer of recordkeeping and potential record manipulation for us to survey.

Moreover, we are concerned that an adverse situation involving a contract monitor could affect a very large number of drug companies and marketed drugs. At least one such contract monitor firm has recently turned up as the common denominator in a number of

seriously flawed clinical investigations, involving several investigators and several drug companies.

In our proposed sponsor/monitor regulations we require that companies employing contract monitors notify FDA of this fact. Because there is no current requirement for notification, it is only by accident that we might discover such arrangements. Our proposed regulations also provide for possible disqualification of a contract research organization if adequate cause is found to exist.

To summarize, Mr. Chairman, our Drug Bureau's current programs for monitoring clinical investigators and sponsors/monitors have produced results that closely parallel earlier findings reported to the subcommittee in March 1978.

While the vast majority of the research we audit is being performed in a generally acceptable manner, we are still finding investigators and sponsors who fail to follow even the most rudimentary standards of good research. We have taken appropriate regulatory action, including disqualification of clinical investigators and recommendations for criminal prosecutions in a number of cases that warrant such action, and we will continue to do so in the future.

In addition, we are attempting to educate sponsors and investigators in good research practices during the course of our audit and through the publication of regulations that meet current needs of Government and private sector.

That completes my prepared statement, Mr. Chairman. We will be pleased to answer any questions that you or members of the subcommittee may have.

Senator KENNEDY. Senator Metzenbaum.

Senator METZENBAUM. Mr. Gardner, this whole record of transgressions, misfeasance, malfeasance, nonfeasance—call it what you will—is so shocking that one is led to ask why.

How do so many academicians, physicians, scientists—how do they find themselves or what leads them into this kind of act, so much of which is unintentional but would appear to be quite intentional?

How would you account for it?

Mr. GARDNER. I wish I knew the answer to that, Senator. I think that many of these people have been accustomed to working relatively independently, unsupervised, and doing what they believe to be correct. They have become accustomed to that mode of operation and believe it is still acceptable practice. It is difficult to believe that is the case. Certainly some of the deficiencies in their practice make it difficult to believe that they could ever have considered such practices to be socially acceptable or ethically acceptable.

[The prepared statement of Mr. Gardner follows:]

STATEMENT OF SHERWIN GARDNER, ACTING COMMISSIONER, FOOD AND DRUG ADMINISTRATION, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Mr. Chairman:

When we last appeared before this Subcommittee to discuss the Bioresearch Monitoring (BRM) Program in March of 1978, we reported some early results from compliance activities (implemented with funds approved late in 1976) to assure the quality and validity of research submitted to the Food and Drug Administration (FDA). We then discussed several case histories of human drug trials that involved both deviations from good scientific practice and disturbing violations of the rights of human subjects involved.

Because the Subcommittee has indicated a special interest in clinical investigations of human drugs and in the monitoring of those studies by drug firms and other sponsors, I will concentrate on these areas of our program in my testimony today.

CURRENT FINDINGS

Since the time we last testified on this subject, we have gained added insight on the scope of the problem, as a result of over 200 procedural or "data audit" investigations of physicians and through over 100 associated inspections of most of the pharmaceutical manufacturers sponsoring and monitoring their work. I am providing for the record an analysis of the findings of these investigations prepared by our Bureau of Drugs. That Bureau also conducts an extensive program of "for cause" inspections of clinical investigators and monitors of investigational drug studies.

The two programs--"for cause" and data audit--are, in our view, closely interrelated and equally important tools for evaluating and bringing about necessary corrections in human drug testing. Both programs evaluate records underlying data submitted to FDA, but one is of a general surveillance nature while the other involves more intensive inspectional work. "For cause" inspections are generally carried out when there is reason to believe that the work of a clinical investigator is faulty or unreliable. Data audit inspections, on the other hand, are undertaken even when problems are not suspected. They are designed primarily to educate and evaluate researchers by making them aware of the most common procedural deficiencies. These audits provide FDA with a broad picture of the quality of drug evaluation in this country. They also give us insight into the types of serious deficiencies that might be probed in greater detail in "for cause" inspections. Finally, the data audit program audits research being performed in support of important new drug applications pending approval at FDA.

Our most recent experience with both programs closely parallels our earlier findings. On the one hand, although we have found a high percentage of procedural deficiencies, the great bulk of the research being conducted is of acceptable quality, and human test subjects are receiving adequate protection. On the other hand, we are still finding a number of investigators whose work represents sloppy science, disregard for the rights of test subjects, and misrepresentation of test data.

We are taking steps, including disqualification of clinical investigators and recommendations of criminal action to the U.S. Attorney, in all cases where such action is warranted. Since we last testified before this Subcommittee, we have disqualified 11 clinical investigators, bringing the total number ineligible to receive investigational drugs to 33. We are currently working on the cases of 29 physicians whose deficiencies are such that disqualification and/or criminal prosecution appears warranted. Only two of these were discussed here last year. A tabular summary of the significant problems found in these investigations will be provided for the record.

Thus, our recent experience only reinforces the earlier findings that some significant deficiencies still exist in the testing of investigational drugs. Regretfully, these problems apply not only to physicians who conduct investigations in their private offices, but also to those doing research in academic institutions and under Government sponsorship. Without identifying the individuals involved, since these cases are still pending, we are prepared to discuss here today with the Subcommittee some details of our findings in these investigations.

ROLE OF THE SPONSOR/MONITOR

It is evident that FDA cannot oversee all of the drug trials conducted under our authority--nor should we. The legislative history of the Federal Food, Drug, and Cosmetic Act makes it clear that the Congress wanted that responsibility to rest with the sponsor of the study, which in most instances is a drug company. Whereas the responsibilities

of sponsors have been defined to some extent in current regulations, these regulations are no longer adequate to cope with present day problems.

Recognizing this, we proposed regulations setting forth the obligations of sponsors and monitors of research in September 1977. At the same time, FDA began inspections using the proposed regulations--both to measure the performance of sponsors and monitors and to assess the merits of the proposed regulations.

The final regulations will require monitoring not only of investigational new drug studies, but also investigational studies of medical devices, biologicals and food additives. They will require personal visits by the monitor to the investigator and encourage the monitor to review source documents to assess the validity of the reports to be submitted to the FDA. The regulations will also require that records be made of these visits and that these records be available for review by the FDA. Finally, they will provide for the possible disqualification of a sponsor or his agents for serious violations of the monitoring regulations.

Through these regulations we hope to achieve better direct monitoring and evaluations by drug firms. We are not, however, turning over the entire job of investigator oversight to the sponsor. Our Bioresearch Monitoring inspection programs are ongoing, and we will continue to conduct on-site investigation of key studies important to the approval of the new

drug application submitted to us. The proposed sponsor/monitor regulations are scheduled to be published in final form by the end of the year.

CONTRACT MONITORS

Possibly as a direct result of our investigative activities and your Subcommittee's continuing interest in exposing poor research practices, drug company sponsors have been employing to an increasing extent outside contractors to monitor clinical investigators. This arrangement cannot relieve the drug company from its legal responsibility to monitor the investigation, and it creates yet another layer of recordkeeping and potential record manipulation for us to survey. Moreover, we are concerned that an adverse situation involving a contract monitor could affect a very large number of drug companies and marketed drugs. At least one such contract monitor firm has recently turned up as the common denominator in a number of seriously flawed clinical investigations, involving several investigators and several drug companies.

In our proposed sponsor/monitor regulations we require that companies employing contract monitors notify FDA of this fact. Because there is no current requirement for notification, it is only by accident that we might discover such arrangements. Our proposed regulations also provide for possible disqualification of a contract research organization if adequate cause is found to exist.

SUMMARY

To summarize, Mr. Chairman, our Bureau Drugs' current programs for monitoring clinical investigators and sponsors/monitors have produced results that closely parallel earlier findings reported to the Subcommittee in March 1978. While the vast majority of the research we audit is being performed in a generally acceptable manner, we are still finding investigators and sponsors who fail to follow even the most rudimentary standards of good research. We have taken appropriate regulatory action, including disqualification of clinical investigators and recommendations for criminal prosecutions, in a number of cases that warrant such action, and we will continue to do so in the future. In addition, we are attempting to educate sponsors and investigators in good research practices during the course of our audit and through the publication of regulations that set appropriate standards.

My colleagues and I will be pleased to answer any questions you or other Members of the Subcommittee may have at this time.

6

Senator METZENBAUM. I am rather new to this subject, but when I see the kinds of violations, misrepresentation of medical history and altered or falsified laboratory work, inadequate documentation, falsified patient consent forms, inadequate consent, misrepresentation of how the consent was obtained, falsified or misleading evidence of Institutional Review Committee approval, one after the other, and there are more, it just really shocks me beyond belief to think that they are responsible, respectable people and, as I gather, in many of these instances, there was not even a monetary consideration involved, there is not any suggestion of bribery or anything to that effect; is that correct?

Dr. HENSLEY. I would like to respond to that if I could.

I have developed a number of these cases and had some hand in preparing this chart.

Senator METZENBAUM. Speak a little louder, please.

Dr. HENSLEY. I have given this some thought myself. I have been involved in the development of these cases, and it had the same impact on me that it has had on you. It is depressing, if nothing else, and I think that I finally came to understand it when I stopped thinking of it in terms of research, because this really is not research for the most part. There are monetary considerations here for the most part.

What we are talking about is a service provided for fee, just an extension of the fee-for-service system. I think that the medical profession perhaps may apply a dual standard. On the one hand, we have seen people who are very, very careful with academic kinds of research, but yet seem to regard this as something less than real research, and I think that may be behind this.

Senator METZENBAUM. What about the reaction of their peers when that kind of thing comes out, or does it come out?

Dr. HENSLEY. There is generally a genuine shock and surprise. We are talking about individuals, we are not talking about researchers generally. There are a few bad apples in every barrel.

Senator KENNEDY. As I mentioned in my opening statement, we have not identified the doctors or investigators, but we do have the chart which would reflect at least the summation of the institutions, as well as the types of abuses that we have encountered. We will refer to the investigators by number. This has been preagreed with the panel from the Food and Drug Administration, which has done a good deal of work in the investigations.

So we will start with what we call investigator 31.

Dr. Hensley, we talked about investigator 31 at the last hearing, and I understand we have several significant developments in the case since then.

As I recall, the investigator worked on drugs for three different pharmaceutical companies: Roche, Knoll, and Endo. The data submitted to Knoll turned out to be an exact duplicate of the data submitted to Endo the preceding year with only the dates changed.

The data in these studies was entirely fabricated; is that correct?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Would you review what Doctor 31 told the FDA inspectors happened to him that caused him to lose his data?

Dr. HENSLEY. Well, Doctor 31 characterized himself as a compulsive worker. He stated that he really had done the studies but he just had so much to do that he felt that he had to take the work with him on a picnic and had the data in a rowboat with him. And the rowboat allegedly capsized. The data went to the bottom in a metal box and was not retrievable. He did admit to us during the inspection that he had falsified the data. He had tried to make it as close to the original as he could, he said, but it was false.

Senator KENNEDY. Now, did this doctor not ask two nurses to corroborate the fact that they were with him when the boat capsized?

Dr. HENSLEY. Yes, he did.

Senator KENNEDY. Were the nurses, in fact, with him?

Dr. HENSLEY. No.

We have an inspection report or report of investigation from the Veterans' Administration. As you indicated, this doctor did work for the VA.

Mrs. J said one day during the fall of 1977, Dr. 31 came to her work area and said he wanted to talk with her. She said her desk was in a public area rather than a private office, and Dr. 31 indicated he wanted to talk with her alone. She said they went into the vacant doctor's office and the doctor closed the door. She said the doctor told her that an investigator from the Food and Drug Administration would be in to see her at 8 a.m., the next day, and

the doctor wanted her to confirm the statement he had made to the investigator that the two families were in a boating accident at a local lake and some of the doctor's research papers were destroyed. Mrs. J said the doctor appeared to be very frightened. Mrs. J said she told the doctor she had never been on the boat with his family and she could not confirm his statement to the FDA investigator, whereupon he became very angry.

I could read a similar statement from another nurse but it is the same type thing.

Senator KENNEDY. Where did Dr. 31 claim to have gone to medical school?

Dr. HENSLEY. The University of Saigon, during the Japanese occupation.

Senator KENNEDY. What did the FDA learn when it tried to find out if, in fact, the doctor had gone to the University of Saigon or to the Paris campus of the University of Saigon?

Dr. HENSLEY. We had quite a bit of help in that from the Veterans' Administration. We were able to locate two or three witnesses, one a fellow who happened to have lists of graduates at the University of Saigon for the appropriate years, and two others who were doctors who graduated in the same class as this physician allegedly graduated in. It would appear that the doctor never went to the University of Saigon.

Senator KENNEDY. Is there any evidence that the Dr. 31 is, in fact, a doctor?

Dr. HENSLEY. Not at all. There is, in fact, a communication from the doctor to the French affiliate of the university where the doctor recently asked the university, "if anybody asks, please say I went there."

No, there is no evidence.

Senator KENNEDY. Was that in French?

Dr. HENSLEY. Yes. That is an interesting point. The two doctors who allegedly graduated with this doctor reviewed the medical diploma of the doctor and pointed out to us that the diploma was written in bad French. The university official in France likewise pointed out the letter was written in bad French.

Senator KENNEDY. All right.

Did he actually obtain a medical license in Ohio?

Dr. HENSLEY. Yes, he did.

Senator KENNEDY. How was he able to do that?

Dr. HENSLEY. Well, as I understand it, from my conversations with the doctor, he attempted to pass the medical boards in the State of Massachusetts 10 times. I believe they were using the FLEX exam. Having failed that, he went to the State of Ohio, where the requirements were much less stringent.

During that period of time, the State board exams were often relatively easy in some States.

Senator KENNEDY. Did he get a license in California?

Dr. HENSLEY. Yes, he did. Apparently through reciprocity with Ohio, and practiced medicine there at the Veterans' Administration for 11 years.

Senator KENNEDY. For 11 years?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Does he still have a license?

Dr. HENSLEY. I believe he does.

Senator KENNEDY. And is he a physician?

Dr. HENSLEY. No, not to the best of our knowledge.

Senator KENNEDY. So, to your knowledge, he may very well still be practicing?

Dr. HENSLEY. I believe he is.

Senator KENNEDY. Well, we have a person who has never gone to medical school, who took qualifying medical examinations many times, and finally passed one in Ohio, and through the process of reciprocity has one in California, who worked in a VA hospital for 11 years, fabricated drug studies for three major pharmaceutical companies, and two of whom were unable to detect any problems. That is a rather extraordinary comment on the system.

Do you know whether the doctor works in the VA system at the present time?

Dr. HENSLEY. No, he does not. I would say about a month after your last hearing, he left the system.

Senator KENNEDY. There are humorous aspects to the story. However, the bottom line is that the man tested drugs in human beings, or claimed to, and submitted the documentation to the pharmaceutical companies, and that data was fabricated. He was able to fool the Veterans' Administration and function as a doctor, able to fool some major pharmaceutical companies and to serve an internship in the United States, and has been able to treat patients. He is not a doctor and did not do the studies. It is an extraordinary and unprecedented story.

One wonders about the nature of the quality of the monitoring on human testing by the pharmaceutical companies as well as the quality of monitoring of the medical profession with regard to its licensing of physicians. It is a dangerous story.

Could we talk about Dr. 24.

As I understand, he is a psychiatrist, and from 1971 to 1978, he conducted a number of clinical studies for drug companies.

How many drug companies?

Dr. HENSLEY. Six companies according to our records, some 12 studies.

Senator KENNEDY. Why did the FDA begin inspection of this man's work?

Dr. HENSLEY. This was one of our routine data inspections, a relatively small study of a psycho active-drug. Our investigator visited the doctor at his office and became suspicious because of the—first of all, doctor's lack of records and his behavior. I think the story is interesting.

The doctor ushered the FDA inspector into a back office, and in the office was a large executive type chair and desk, and nothing else, and the doctor was seated in the executive chair and had a kindergarten size chair brought in for the FDA inspector. He then proceeded to turn the thermostat down as far as he could, and throughout the interview he turned it up and down, up and down, and made the inspector rather uncomfortable.

More importantly, though, he was unable to provide records that would show a study was ever actually done. I do not know if there is anything personal in this or not, but subsequently the FDA inspector took an interest in the case, and he proceeded to check

the corporate records on the doctor, this small practice the doctor was in, and learned the doctor was being sued by a patient and also, I think, by the State of California.

There were allegations also of fabrication of data by one of the office nurses.

Senator KENNEDY. In the FDA report on Dr. 24, the conclusion of which was, and I quote:

In a gross synopsis, we have been unable to substantiate that most of the patients reported by Dr. 24 to be involved in specific drug studies were actually on those studies.

Let me just read from some of the deficiencies. I am reading specifically from the report:

No consent forms were located for any of the 31 patients even though the protocol specifically called for the signed consent form, and there were no records to substantiate the clinical chemistry report submitted in support of the study. In fact, some laboratory data submitted in support of the Marion study in 1977 were found to be identical to those previously submitted in 1976 with the Winthrop and Upjohn studies.

Then there is the exhibit which would show absolute identical results.

Then it continues:

There were no records to substantiate the subject office visits, drug administration or drug accountability. One subject was apparently in Texas when this study was conducted and thus could not have been properly involved in this study. An examination of drug supplies found in the doctor's office indicated bottles had been opened and apparently been used to dispense medication.

And so on.

Dr. HENSLEY. I would like to make a comment about that drug accountability if I could.

This was the first time we encountered the flush method of maintaining drug accountability. We learned from an office assistant, a research assistant, that the way the doctor got the pill count to come out correct was to count the correct number of pills the patient should have taken and then to flush them down the toilet.

Senator KENNEDY. And then what?

Dr. HENSLEY. Flushed them down the toilet. That way the monitors were kept satisfied, I guess.

Senator KENNEDY. Maybe at this point I might add Ms. Findlay who is the former wife of Dr. 24, to come to the table.

We appreciate your cooperating with the subcommittee.

I think from the opening statement and comment you can understand what we are really trying to come to grips with and why this type of issue is very important to millions of Americans, so we are enormously grateful for your help and assistance to the Committee.

As I understand, you were married to the doctor in question here.

Ms. FINDLAY. Yes.

Senator KENNEDY. Did you work for your former husband on any of these studies during 1970 to 1975?

Ms. FINDLAY. Yes, I did.

Early in 1970, I believe, until 1974. I was not involved in the studies you were specifically mentioning, but in one earlier than that.

Senator KENNEDY. I see.

How would you characterize the conduct of the study? Could you do that for us?

Ms. FINDLAY. Well, it is very difficult to put in words. I do not really know how he first got involved in becoming involved in research. I believe he was approached by someone in one of the drug companies, and he was offered a very small research study which, at the time, I was not married to him, I worked with him. He proceeded to let a certain amount of time elapse, for it was not really possible to conduct the study as it was supposed to be conducted, and as the time span was becoming shorter, he asked my help and several of the other people who worked at the time at the State Hospital to assist him in filling out forms which were required for the study, which were mainly nursing reports like observation of the patient, weekly observations of the patient by nursing staff, this sort of thing, whether they were improving or indications of their behavior.

And at the time, it didn't seem like such, you know, a big thing. It was kind of like just a request and it was done.

Then, later on, another research project by the same drug company was brought to him, and it was on a larger scale. And I did not want to be involved in it. But at the time we were married, and again he was a very busy man and he let his time fall short and asked me, in order to help save his reputation, to please assist him in finishing this project which, if you would like, I would go into how it was done. He did not break the code that was given, you know, the drug company provides a code for these—in case of emergency, if the patient becomes ill or whatever, to determine which drug they were receiving. But he opened the capsules from this study in the bottles and determined somehow, I don't know how exactly he determined it, but determined patient No. 1 was the placebo, patient No. 2 was the study drug or however, and this was written down on a piece of paper like patient No. 1, placebo; patient No. 2, study drug; so on throughout the study.

He gave me a sheet which he had written which had lab normals on it, which were basically what were the range of normal urinalysis, or blood count, or whatever was required by the study, and he asked me to fill out for each of the patients lab normals which I determined to be within normal range for each patient.

Senator KENNEDY. Well, now, that would really be faking the report, would it not?

Ms. FINDLAY. Yes, it was faked.

Senator KENNEDY. Because you wouldn't know—

Ms. FINDLAY. There were no lab reports done. The way the patients were selected, he selected patients from his private practice, people who came into the office to see him, to seek psychiatric help, and had a sheet they called a face sheet he put in his office records which had their name, address, age, who they were referred by.

Senator KENNEDY. How frequently would you have to fake those reports?

Ms. FINDLAY. Well, the drug company was requesting patient information be submitted in groups of, like, 10, say 10, and he would have everything dated so that, say, 10 patients began the study at the same time, and they completed it approximately at the

same time, and those 10 records were submitted, and another 10 were begun shortly thereafter.

Senator KENNEDY. But, in fact, there were no patients for those studies?

Ms. FINDLAY. No. The drugs, the capsules or pills themselves were done similar to Dr. Hensley saying that they were counted out, as if the patient had taken x number of pills every day as required, and those were dispensed of, and then the remaining drugs and bottles were returned to the drug company.

Senator KENNEDY. What about the EKG's? Did your husband use legitimate EKG's?

Ms. FINDLAY. No, he did not. The monitor for this study—well, EKG's, according to the protocol, were supposed to be done. They were not requested to be seen until after the study was completed, and at that time my husband went to a woman who worked at the hospital he was affiliated with, whose son happened to be a patient of hers, and I do not know what story he gave her in requesting EKG's, but he requested copies of normal EKG's from her. Again I do not know what he told her. Then he brought them home and correlated them as if they were prestudy or poststudy EKG's for the same patient. The names were written on the top, the names were deleted to begin with, and names corresponding to the patients were put onto EKG's.

The monitor came out and looked at them, and I assume he was satisfied. I do not really know.

Senator KENNEDY. Did your husband ever break the code so that he knew which drug was in each bottle?

Ms. FINDLAY. Well, I do not know if he took the drug to someone he knew to have it analyzed or whatever. He broke the code by analyzing or looking at the drug inside the patient capsules rather than opening the written code. I do not believe he ever opened the written code.

Senator KENNEDY. Now, I understand that after a period of time, working at the hospital clinic with your husband, a lot of the work moved to your home when you became pregnant?

Ms. FINDLAY. Yes.

Senator KENNEDY. How did this work?

Ms. FINDLAY. Well, after this second study, I told him I just could not conscionably do this any longer, and I did not want to be involved doing anything like this. And another drug company approached him with two additional studies, and it was considerable financial remuneration involved, and I told him that, in my opinion, he should definitely do the study legitimately, there was enough money involved so he could pay the people necessary to do this. He said OK, that is what he would do, do not worry about it.

Well, it came down to the last minute again, and the study had not been done, or both studies, there were two studies that were supposed to be ongoing at the same time, and at the time I was pregnant and I had six children at home, and this is my financial support here, so I decided that maybe I had better at least get this squared away and not have his career ruined, so he was giving me the idea that this was very, very important to be done.

So, under great duress, I completed the data on two additional studies, the next two studies, and after that I just absolutely re-

fused, will not be involved in any more. I heard mention that 12 studies were done altogether, and so I do not know who or how he got those other studies done because we proceeded to separate and divorce, and I was no longer involved with him in that type of thing.

Senator KENNEDY. Were there reports from the drug companies, do you know?

Ms. FINDLEY. Definitely. After the first study, the drug company started sending him to medical conventions and psychiatric association conventions, and they made an exhibit of the summary of the drug research, and we had an exhibit—he had an exhibit at several conventions and proceeded to, after the second study, to make a professional movie in which he was the star of, and then was used in medical education and training of physicians, like drug companies often provide educational settings for training for physicians, and this was also used as a training film and also marketing department used it in their promotion of the drug.

Senator KENNEDY. Do you remember the drug companies?

Ms. FINDLEY. Yes. Would you like me to name them?

Senator KENNEDY. Yes.

Ms. FINDLEY. Sandoz Pharmaceuticals were the first two studies, and then Lederle Laboratories were second two studies that I was involved in.

Senator KENNEDY. Did the companies themselves ever come to monitor, to your knowledge, the so-called studies?

Ms. FINDLEY. The second Sandoz study, there was a monitor, and most of that type of thing, the interchange between monitor and my ex-husband, I was not present, but I guess he was able to satisfy whatever questions were presented to him. I do not know that he ever asked to see correlating patient records, you know, substantiating lab reports or anything like that.

Senator KENNEDY. The raw materials?

Ms. FINDLEY. Right. The only thing that I know of was that he did ask for EKG's, and that is when he got those—

Senator KENNEDY. Those were falsified, and yet they were able to at least, to your knowledge, to satisfy the companies?

Ms. FINDLEY. Correct.

Senator KENNEDY. How do you feel now after all this period of time? What is your own reaction?

Ms. FINDLEY. Well, I have always felt very uncomfortable about being involved in it. I felt pressured, and I do not think that is an excuse for anything that I did, but I feel a little better getting it out in the open, and I think that there should be better safeguards.

It seems to me that what happened was fairly blatant and fairly obvious, and I did not understand, especially after two or three studies had gone by, why some question was not brought out sooner, for him to go on and do six or seven more studies—

Senator KENNEDY. Along the same line without interruption?

Ms. FINDLEY. One of the reasons the investigators—at least this is what they told him—they liked him doing research was that his dropout rate was so low. Usually in investigating psychiatric patients especially, first of all, you have difficulty in getting their consent and, second of all, they are kind of, you know, they are not usually all there, or they would not be seeking psychiatric help. So,

usually the dropout rate in psychiatric oriented research was very high. His dropout rate was very low, and that to me would be a big point right there. But different companies continued to come to him for research.

Senator KENNEDY. Is your husband practicing today?

Ms. FINDLEY. Right now he is in the Navy practicing as a physician for the Navy.

Senator KENNEDY. I want to thank you very much for your cooperation and your help to us. I know it is not an easy task to review that past, and I think it is going to be helpful to us in trying to develop a program.

Ms. FINDLEY. Thank you.

Senator KENNEDY. Thank you very much.

Dr. Hensley, the next series of three investigators are all people who worked for academic medical centers, and as I understand it, are all people with substantial reputations in the field they work in. These would be Drs. 12, 16, and 10.

Let us begin with Dr. 12. As I understand it, he did human testing for several companies on several drugs.

What did inspection of Dr. 12 reveal to the FDA?

Dr. HENSLEY. Inspection of Dr. 12 is very similar to inspection of Dr. 31 in that I would say that the FDA inspector and myself had something of a good time in the record room at the hospital comparing the patient charts to the hospital records, and their records in the hospital bore little or no resemblance to the patient charts. And based upon patient interviews, it would appear that most, if not all, of the case reports had been falsified.

Senator KENNEDY. Now, there were, as I understand it, rather serious discrepancies between the case report forms submitted by the doctor and what was actually recorded on the patient's chart. Actually, this is a copy of the case report form and also the patient chart.

On patient No. 1, it has incision and drainage on July 31, 1978, and then the patient's chart has no surgery on July 31, 1978.

Then, on the case report forms, it has tylenol for August 2, 1978, and the patient chart has no mention of tylenol.

Then it has, or the case report form has no medication within a 4-hour observation period, nausea and vomiting on August 2, 1978, and the patient chart has pain medication at 9:30 in violation of the protocol, and there is no mention of that.

Patient 48 has left knee surgery while patient records has no surgery. It has patient 48 on study medication, and in the patient records, no medication.

You could go on through a number of the different patients to show the difference between the report form and the patient chart.

Dr. HENSLEY. That is correct.

Senator KENNEDY. Were those the kinds of misrepresentations or distortions that you found on your examination of Dr. No. 12?

Dr. HENSLEY. Right. I believe you have handed out a chart on Investigator No. 12 that compares case report forms to patient charts. I think there are some extreme examples here, too.

For example, on the second page of that, Patient 10055, "surgery on 11-13-78 with study drug given at 12 a.m. on 11-16-78."

When we looked at the patient chart, it says "Patient's jaws wired shut, unable to take capsules." Was on liquid medication. "Discharged on 11/15/78, never given study drug."

We interviewed that and, of course, the patient denies ever having participated in the study and states that the signature on the informed consent was a forgery. That is generally the case. We have interviewed many of these cases, and data is fictitious, and signatures are forgeries.

Senator KENNEDY. As I understand it, 57 other patients who were reported to have had surgery whenever listed in the anesthesia recovery room log on the dates that were recorded in the case reports?

Dr. HENSLEY. That is correct.

Senator KENNEDY. What does this mean?

Dr. HENSLEY. Well, it has to be taken in the context of the rest of the inspection. Some of those 57 do not exist. Some of those 57 never had surgery, and some of the 57 may have had surgery on other dates, but it bears little resemblance to what the doctor reported in the case reports.

Senator KENNEDY. What is your conclusion about the work that was done?

Dr. HENSLEY. It is worthless, absolutely worthless. It is, by the way, a pivotal study.

Senator KENNEDY. A pivotal study by a prominent physician in a major academic institution?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Now, Dr. 16, also a prominent physician at University Center is widely respected. As I understand it, FDA conducted inspection on a Pfizer drug.

Would you tell us why this study was conducted and what the results were of the inspection?

Dr. HENSLEY. Inspection was initiated because the doctor had conducted a study that was considered very important, if not pivotal, in the approval of new indication for the Pfizer drug. We included this study in a number of other studies that we listed for the doctor, stating we would inspect some five studies.

The doctor, upon learning this, became somewhat apprehensive to try to find out exactly what we were going to concentrate on, why we were doing the inspection. We had learned, of course, from the medical officer in the Reviewing Division who had pointed out this study to us that the data looked too good. We did not want to tell that to the doctor because, if nothing else, we did not want to offend him. At that point, we did not know what was going on.

The doctor subsequently being unable to pin down why we were coming, telephoned an official of the Bureau of Drugs and confessed to falsifying portions of that study and another study. We subsequently initiated the inspection, and what we learned was that the doctor was actually confessing to falsifying chest X-rays on these two studies, chest X-ray reports. These drugs are cardiovascular drugs, so the chest X-ray is very important.

In addition, however, we have found very serious discrepancies between case report forms and patient charts, and I think you have handed out a table here on Investigator No. 16 that deals with those kinds of observations.

Senator KENNEDY. Now, this particular physician has published over 200 scientific papers, I understand?

Dr. HENSLEY. That is correct, 211.

Senator KENNEDY. Do you know whether any of the papers were based on seriously deficient work?

Dr. HENSLEY. Yes. A particular study that we were interested in was published, and also another one had admits to having falsified, at least in part.

Senator KENNEDY. You mean they published the papers based on the work, and now it turns out that the work seems to be seriously deficient, at least in part?

Dr. HENSLEY. That is correct.

Senator KENNEDY. What is your conclusion about the work done by Physician No. 16?

Dr. HENSLEY. I think that my conclusion has to be a personal one at this point. We obviously have found some very serious problems. It is possible, because of the fact that the doctor delegated responsibility to fellows for one thing or another that some of his work might be worthwhile, but I would prefer to discount all of his work.

As far as I am concerned, this kind of thing is like a touch of death. There is no such thing as a little fraud. I think we have to throw it out.

Senator KENNEDY. Was there not an audit by Pfizer on one of the drugs?

Dr. HENSLEY. Yes, there was.

Senator KENNEDY. You have had an audit, FDA audit, as well?

Dr. HENSLEY. Right. After our FDA inspection, Pfizer initiated an audit, and sent us the results of their audit.

Senator KENNEDY. How does the Pfizer audit vary from the FDA audit?

Dr. HENSLEY. It varies in a number of places. It would appear to me that the Pfizer audit was probably conducted with some haste, because there are a number of serious differences between what was actually in the patient charts and what Pfizer people report. We have a memorandum from our inspector in California who participated in this inspection, comparing the two.

Senator KENNEDY. Could we go to Doctor No. 10? Why did you inspect Doctor No. 10?

Dr. HENSLEY. Doctor No. 10 was an interesting case, in that this is a very inexperienced researcher in the sense of pharmaceutical research. He is associate professor now, I believe, having been recently promoted. He was approached by a pharmaceutical company to do a study. They seemed satisfied with the study for the first 6 to 8 months, and then began to take a hard look at it, and discovered that electrocardiograms were apparently fictitious, and then came to us.

I think in all fairness I should say within 2 weeks of the time they discovered that, they came to us. We inspected the doctor, looked at both studies he had done for this sponsor, and those were his only two studies, I might add, with investigational drugs, and found something very interesting.

It would appear that in fact the EKG's were fictitious, but the rest of the study, the first study was letter perfect. The second study, on the other hand, was terribly sloppy, but there was no

fraud. I think it probably comes back once again to delegation of responsibility.

The doctor maintains that his help had been responsible for most of these things, and on the one hand, the help having created fictitious data, and on the other hand, the help having been responsible for sloppy data.

Senator KENNEDY. But that had not been picked up, the sloppy data?

Dr. HENSLEY. No. It had not. The pharmaceutical company could have picked up on the sloppiness of this study only by comparing the case reports to the patient charts.

Senator KENNEDY. But the EKG's were falsified?

Dr. HENSLEY. Yes, they were.

Senator KENNEDY. By whom?

Dr. HENSLEY. The doctor alleges they were falsified by a study nurse. I have interviewed the study nurse, and she admits having done that. The question now is who told her to do so, and we still have not resolved that. I think the bottom line is here though that the doctor is the investigator, and he is the one who signs the agreement, the statement of investigator form, and he is responsible. He also was the one who received the EKG's from the nurse and inserted them into the case report and sent them to the sponsor.

Senator KENNEDY. Now we have the case history of three prominent university professors, all of whom have done work characterized either as seriously deficient, if not outright fraudulent. The question is why, or what is the motivation here? Why would people want to do that, and I suppose the underlying question is the seriousness of the violations, and why we should be concerned about these problems?

I think this is a very serious question. The next two cases are different kinds of cases. They are prominent physicians who did not follow, and did not care to follow, the FDA's procedures.

The first is Doctor 9, and the second is Doctor 30. As I understand it, the FDA has had a long running problem with Doctor 9, problems that have been marked by his disregarding the FDA's regulations, failure to provide progress reports as required, failure to maintain records properly, failure to comply with protocols, failure to respond to FDA inquiries, failure to live up to the commitments made to FDA. Is this all correct?

Dr. HENSLEY. That is correct.

Senator KENNEDY. So would you briefly describe how this pattern of behavior developed, and specifically what was FDA's experience with this doctor over the years? Perhaps you would just use some specific examples to highlight it.

Dr. HENSLEY. This physician is a very prominent psychiatrist. He has published over 400 articles, a couple of books. As such, I think he had entree into the Division of Neuropharmacology at a level that perhaps others would not have had. And early on, as in the late sixties, early seventies, I think had something of a special relationship perhaps with the Division of Neuropharmacology, in that he obtained IND's for investigational drugs—and in this sense the doctor is both sponsor and investigator—and then proceeded to use them as he chose, and ignored the requirements that he report

at least periodically his use of the drug and what is happening with it.

It came to a head, I suppose, in 1974, when the doctor was asked once again for a progress report on one of his investigational drugs, and did this time send in a report, which I think was probably a one- or two-line letter, accompanying a reprint of a publication that he had recently presented. It mentioned some 300 patients on the investigational drug, and alluded to others.

The Neuropharmacology Division became alarmed, sent back a vigorous request for more information. The doctor promised to comply immediately.

Then, the next several years were repetitions of those letters, the doctor being asked, and the doctor promising to comply, and the doctor not complying. To this date we still have not received reports on those 300 patients.

One problem that came along with this same drug, virtually at the same time, superimposed on this, and ought to be talked about, is a serious adverse effect, a life threatening adverse effect associated with that drug.

The doctor was informed, in August 1974, that there was such a problem, and was asked to please restrict the use of the drug to patients who absolutely could not do without it, so-called hardship cases. The doctor promised he would. But within a month FDA was copied on a cable from a Swiss supplier of the drug, where the doctor was quoted as having told his Swiss supplier that FDA had given approval to go ahead and treat all 400 of his patients. FDA naturally took exception to this, and told the supplier they would prefer that the drug not be sent, and this precipitated the great luncheon meeting that I think is almost legend at FDA now, where the doctor came in, on a chartered plane, and brought a catered lunch for officials at the Bureau of Drugs and Neuropharmacology Division, and came in, of course, with his attorney, one of the more prominent attorneys locally here, and made numerous assurances, which again, of course, were not complied with.

The next couple of years we have a series of memos back and forth, letters, where the Agency is trying to get the doctor not only to tell us what he is doing with the drug, but to restrict his use of the drug. There are a couple incidents that are worth noting.

One incident where a doctor, where the doctor allegedly called from Chicago, talking to the Commissioner, and said: "Commissioner, could you tell me why I should not go on television in five minutes and tell the country what an awful job the FDA is doing, and why they are not letting me treat my patients?"

The Commissioner, of course, passed that along to HFD 120, who apparently modified this stand on the distribution of the drug somewhat.

Another occasion, as the Agency began to toughen up the response, and threatened to terminate the IND, the doctor allegedly threatened to land a helicopter on top of the Parklawn Building where we are headquartered, with most of the prominent people in his practice, and let them tell the Commissioner and the Director of the Bureau of Drugs what they thought of the idea of termination of the IND.

Subsequently, however, after a lot of grief, I guess, the IND was terminated in February of last year, I guess, within 1978, and I happened to be doing inspection of the doctor in May of 1978, and happened to see an investigational drug being dispensed from the pharmacy—

Senator KENNEDY. How long had this been the attitude of this Doctor Number 9?

Dr. HENSLEY. Since day one.

Senator KENNEDY. 1974?

Dr. HENSLEY. Since day one, it goes back into the early seventies.

Senator KENNEDY. There is an FDA notation about this particular case that you referred to, and I quote: this is a case history of how we should not regulate an IND holder. Doctor 9 has been unresponsive to requests for information, has not filed progress forms or reports, has not kept records. In spite of this, we have issued new IND's, allowed new studies on older IND's, and in general been lax and irresponsible in enforcing our regulations. We have much blame to bear for this sorry record.

What about it, Commissioner Gardner, would you comment on this? We have just heard a long pattern of neglect by the FDA regulations. How could this be? Why has not firm action been taken? This has been a pattern that has been going on for several years.

Mr. GARDNER. I think I would agree, and be quite strong in my language about the marginal notation that you cited. I think that is totally inexcusable a practice for us to be so patient—although I would not even use the word patient in this instance.

It seems to me that our response ought to have been much more swift and vigorous, after the first or second opportunity, that is all you get, one bite at the apple.

Senator KENNEDY. He got several bites, from different apples.

Mr. GARDNER. He had several apples, Senator.

Senator KENNEDY. What is the situation now? Have you terminated his opportunities for doing research on IND's?

Dr. HENSLEY. I can more appropriately respond to that. Yes, we are very close to that.

Senator KENNEDY. Very close to it?

Dr. HENSLEY. Yes. There is a two-step process, or two-step procedure in the disqualification process, the second one being in the Commissioner's office, where the doctor gets—

Senator KENNEDY. How far away would you say we are?

Dr. HENSLEY. The last step is within 2 weeks.

Senator KENNEDY. Is this the most notorious case of this sort, of ignoring procedures of FDA?

Dr. HENSLEY. I would say it is the most flagrant case I have ever seen.

Senator KENNEDY. What we are talking this morning, even though there are some records where they have gone back over a period of years, are the results of your current investigation?

Dr. HENSLEY. That is correct. This chart of 29 represents people we are presently taking action against, and of course, your staff added two others to that.

Senator KENNEDY. If I could have Stephen Blythe and Karen Test, who worked as research assistants for Doctor 30, to come forward.

These two witnesses were laboratory assistants for Doctor 30. You were graduate students at the time, is that correct?

Mr. BLYTHE. I was a graduate student.

Ms. TEST. I was——

Senator KENNEDY. You will have to bring the microphone closer.

Mr. Blythe, I am interested briefly in the description of the tests conducted by Doctor 30 on a drug which had not received the clearance of the FDA for testing in human subjects. I would like, if I could, to do it chronologically, briefly and consistently, if we could. Would you describe what you do in the laboratory as a laboratory assistant, from the time the bottle with the chemical arrives, which I understand had a bright orange label, and what did the label say?

Mr. BLYTHE. I started working for Doctor 30 in June of last year. Most of the studies that I was involved with dealt with laboratory rats. I was only peripherally involved in studies dealing with humans.

One of the studies involved a particular type of intravenous feeding solution which he had been using for approximately 2 years in patients. I first became curious about the solution when I saw one of the other employees of Doctor 30 removing from the bottles bright orange labels which said "for animals or in vitro use only, not for human use."

I was asked to remove labels on these——

Senator KENNEDY. The labels said not for human use?

Mr. BLYTHE. Bright orange labels on the side, it said for animals or in vitro use only, not for human use.

The labels came off very easily, with a little acetone.

Senator KENNEDY. What did you do with the labels?

Mr. BLYTHE. Threw them away. I said I would not have any part in it, that I did not feel comfortable——

Senator KENNEDY. Well, I think the point is, was the material used in humans?

Mr. BLYTHE. Yes, it was used in humans, and I was assured that it was okay, that Doctor No. 30 had been issued an IND by FDA, and that he was an approved sponsor for this product.

Senator KENNEDY. Who gave you the information that it had been okayed by the FDA?

Mr. BLYTHE. Initially his employees, and then he many times also gave me that assurance. I was more than a little curious about the product——

Senator KENNEDY. Just to get back again to the human subjects, can you tell how many human subjects were actually involved in this?

Mr. BLYTHE. I do not know the exact number.

Senator KENNEDY. Approximately?

Mr. BLYTHE. I would say 30 or 40.

Senator KENNEDY. Thirty to forty?

Mr. BLYTHE. I did not accept this answer that I got, because the whole ambience of the research group, there was one of exploitation of the patients.

Senator KENNEDY. Of what?

Mr. BLYTHE. Exploitation of the patients. Exploitation of the patients. I felt there was not very much respect for the rights of their patients. Then about the middle of November of last year, Karen called the Knoll Labs, the company that was providing the substance—the bottles had an expiration date on them, which was the end of November——

Senator KENNEDY. Now, if we could, Karen, could you tell us about the call?

Ms. TEST. Doctor 30 instructed me to call the company and ask if there was any way that we could get approval to use the drug beyond the expiration date. That is the reason I called, and I talked to somebody from the company, and it came out we were using this on people, and she was very shocked to hear this.

Senator KENNEDY. The person that you talked to at the drug company was shocked?

Ms. TEST. Right.

Senator KENNEDY. Why was she or he shocked?

Ms. TEST. They. They were shocked because it was not meant to be used on human subjects, as it was labeled as such, and they never instructed the doctor to use it that way. At that point I hung up. She did not want any more information.

Senator KENNEDY. So then you called, did you call Mr. Blythe?

Ms. TEST. Well, I informed Steve about the phone call, and we became a little bit more suspicious at this point, and Steve then got in touch with the FDA, and he had a series of communications with them about the matter, which of course aroused her suspicion more, and at pretty much the end of this we were sure that he was doing something he just had no right to do.

In the meantime, we had also been in touch, or Steve had been in touch with an administrator in the hospital. I talked with a pharmacist about the matter, who was aware of the problem. I was surprised to find out he knew about it. I was trying to be very careful in approaching him, because I thought I did not want to let something out, to start a rumor of some sort.

He said, oh, sure, I know about it, it happened. If we had had an on the spot check, we would have been in trouble, and that kind of thing. In fact, he and a coworker of Doctor No. 30, when they realized that this substance was expired—it turned out that Doctor 30 wanted to use it beyond this point without getting any kind of approval, and they told him not to stop, and they forced him to go to another company to manufacture this solution.

Senator KENNEDY. Let me ask Mr. Blythe, did you at some time make a determination that it was not approved?

Mr. BLYTHE. Yes, Mr. Chairman. After Karen's call to the McCall Laboratory, I thought perhaps the most direct thing to do would be to call FDA, and simply ask them if the material was approved for human studies.

I made an initial telephone call to FDA, and as happens, I was put through about 20 different people to get to the right place. I was initially put through to what I guess was the records room, and the person there I assume thought that I was calling from inside, because he provided me with some information which I later found out he should not have. But I asked what the status of

the drug with this particular IND number was, and he said the status of that was that it was on hold.

I said what does that mean in terms of human studies? He said, well, that means that it is not approved for human use.

I thanked him. And was looking through further data and protocols, and things on the study, and the same drug was also referred to with different IND number in one of the proposals that was sent to the Human Subjects Committee at the hospital, and I did not know whether this was a typo, or whether it was just the wrong number, or perhaps the drug had been assigned a new IND number.

So I tried calling FDA back to find out if indeed that number was the same product.

Senator KENNEDY. Did you find a letter that indicated that it had not been approved?

Mr. BLYTHE. Yes. What I did after that was, we had found some letters, some correspondence between the McCall Laboratories, and Doctor 30. One of the letters, dated April 1, 1977, from Doctor 30 to the McCall Laboratories, addressed to the person who developed these solutions starts out saying that these dog experiments are eating up these solutions at a rapid rate, and again I would appreciate getting up a followup supply released as soon as possible.

Well, I had done the background reading on this project, and I had read nothing of any dog experiments, and I asked the laboratory manager, who had been working with them for 6 years, he said, no, he had never done dog experiments. We do not have facilities to do dog experiments.

Senator KENNEDY. He was asking for more of this substance on the basis of using them in dogs, and they were being used on human beings?

Mr. BLYTHE. Exactly. Also, in the file was something from the McCall Laboratories, from a person there, and the first sentence says, to confirm the solution we sent you was for use in animals only, and this was April of 1977, and also in the files was what I assume was the last correspondence from the FDA, and I was later told that was the case.

He had applied for a sponsorship, IND number, sponsorship to do the study, and I do not believe he was funded by the company, but he was doing it for his own reasons, in that he had received the IND number, but permission to use it in humans was denied.

The next thing I did was to call up this person at the McCall Labs, who this correspondence had been with, and just say, look, I might be making a fool out of myself, but I want to know if the stuff is approved for human use or not. This was about 2 weeks after Karen's telephone call. This person sighed heavily, and said I just talked with Doctor 30 2 weeks ago, and he assured me up and down that this material had never been used on human beings.

So we pretty much knew for sure at that point. Once again I tried to get information from FDA about this other IND number that I had seen. They would not give me any information. They said it is privileged information. I said what I wanted was to know whether or not a product had been approved for human use.

They said we cannot give you that information. I said, what if I were a member of the Human Subjects Committee, and they said

well, we still could not. I said how can you get that information? They said you have to get it from the investigator. I said you mean I would have to depend on the investigator's integrity then? They said that is correct.

My conversations with some of the people at the FDA—well, eventually somebody from FDA—I believe it was Mr. Charles Pre-diman, called me back, and said he could give me some more information if I felt there was a problem with the product. I talked with him, and he said that Doctor 30 should be careful if he started to use this product, because FDA did make random inspections. I told him that would be a good thing to happen. He thanked me.

And a week later, the Boston FDA, one of the people from the Boston FDA office came out and looked at the files, and Karen and I thought that would be an appropriate time to submit all copies of these letters and things to the Human Subjects Committee, and submit our letters of resignation.

Senator KENNEDY. How did you feel when you learned that you had been giving a drug to human subjects that had not been cleared for human subjects?

Mr. BLYTHE. We had not actually been in the administration of the drug, so I do not think we felt any problems with that. In fact, we were trying to clarify the issue. We, of course, felt some degree of abhorrence that it was going on.

Senator KENNEDY. What about the study itself, how did you feel about that?

Mr. BLYTHE. Well, I was not particularly impressed with the quality of the research that Doctor 30 did. He would make statements in public, and then come back and ask his laboratory to document those statements. He would say, well, do you not feel this solution really is harmless, after all it is just protein, and I would answer, no, I honestly do not think anything would happen, although I am sure that was the stand people would take because, as with thalidomide, without knowing that kind of thing—

Senator KENNEDY. Well, thank you very much.

Commissioner Gardner, how serious a problem is it when investigators proceed with test drugs without approval of FDA? In this case no one was hurt, but how serious a violation is it to proceed without approval, or in the face of specific decision that the investigator should not proceed?

Mr. GARDNER. Quite a serious violation.

Senator KENNEDY. I would think so. It is an appalling violation.

Mr. GARDNER. Yes.

Senator KENNEDY. It seems to me that that gets to the heart of the responsibility of the agency, in terms of being able to make the judgments based on sound scientific information and testing. When there is prohibition, as there was in this case, and the researchers just get young researchers to remove labels, and uses materials in human subjects, and obviously conceals that from the company itself, as indicated from their letters where they are talking about dog experiments eating up the supply, that seems to me to be an appalling situation.

What is your reaction? I mean how often does that occur? That get the kind of violation? It involves both, I would think, medical

ethics. What can be done about a serious breach of medical ethics in this type of a situation?

Mr. GARDNER. Would you like to respond?

Dr. HENSLEY. I can respond to that. You are talking about a problem with ethics. I do not think the answer is in legislation. I really do not think you can legislate ethics or morality.

I think that the agency's response on this, while it may have been deficient, made a certain amount of sense, in that the people involved in making the decisions on this case felt that perhaps the institutional review board at the local hospital might exert some reasonable oversight.

And, as I think you have—I believe the new drug act makes some provision for the use of the institutional review board along these lines. I think that kind of peer pressure really has to be exerted.

Senator KENNEDY. Of course, in this case, they were lied to, as well, I guess.

Dr. HENSLEY. That is correct.

Senator KENNEDY. As well as everyone else?

Dr. HENSLEY. Absolutely.

Senator KENNEDY. The final set involves a series of studies that were done by clinical investigators who were retained, not by pharmaceutical companies, but by independent testing laboratories who were themselves retained by pharmaceutical companies. In these cases day-to-day responsibility for monitoring was that of the independent testing laboratory, and we will explore what the responsibility of the pharmaceutical company is when it hires such a laboratory.

Dr. Hensley, the first firm I would like you to focus on is Bio/Basics. As I understand it, the FDA has conducted a field investigation of Bio/Basics. Why was that begun?

Dr. HENSLEY. The investigation was begun because of allegations made by one of the physicians we discussed at the last hearing, a doctor who had been contracted with by the contract monitor, as we refer to these firms. to perform two studies of investigational drugs. We had found serious problems.

He indicated the contract monitor was aware of those problems, and, in fact, some of the questions we had about his work, those had been the idea of the contract monitor. Consequently we decided rather than taking action against the doctor at that point in time, they would investigate the contract monitor, and try to determine whether this was true, and if it was, whether or not there was a pattern of behavior.

Senator KENNEDY. How many investigations were you involved in?

Dr. HENSLEY. We have investigated, I believe, nine physicians.

Senator KENNEDY. Can you describe the deficiencies for us?

Dr. HENSLEY. These 9 physicians were involved in, I believe, 12 studies for 2 pharmaceutical companies who had contracts with the contract monitor. The deficiencies ranged from the appearance of overt fraud, as we have discussed with Investigator No. 31, for example, to at least extreme sloppiness, with apparent alterations, retrospective alterations being made in case report forms, for no apparent reason.

Senator KENNEDY. As I understand, you found deficiencies in all of the eight that you investigated?

Dr. HENSLEY. I should correct that. We found deficiencies in only eight of the nine.

Senator KENNEDY. Eight of the nine?

Dr. HENSLEY. Yes. I would say we found deficiencies in 11 of the 12 studies.

Senator KENNEDY. In 11 of the 12 studies, and 8 of the 9.

You were looking for work that was basically on two drugs, as I understand it, one from Bristol-Myers, and the other from Ortho; is that correct?

Dr. HENSLEY. That is correct.

Senator KENNEDY. You picked what you considered to be the most significant studies for each?

Dr. HENSLEY. Yes. We did not start out to do that. We began by doing a general inspection, back in October of 1978, trying to find out what the contract monitor knew about the problems with the doctor mentioned initially, with Doctor No. 3. We have not talked about—well, the physician also discussed at the last hearing.

And based upon that we determined that we really ought to look at more, and rather than fishing around, we decided to look at pivotal studies, or if not pivotal, strongly supportive studies for two NDA's in question. Those NDA's by the way, had been submitted to the agency in October or November of 1978.

Senator KENNEDY. As I understand it, the most serious case involves Doctor 3, who did studies for several different companies; is that right?

Dr. HENSLEY. That is correct.

Senator KENNEDY. Why did FDA begin inspection of him?

Dr. HENSLEY. That was my idea initially. I had run across Doctor No. 3 long before allegations were made by the physician with respect to the contract monitor, and determined we should look at him because of the volume of work he was doing, and also because of the lack of placebo responders; he was doing pain studies, and of course, in the course of looking at data, you would expect to see a certain percentage, certainly at least 15 percent of patients who were responding to placebo.

We scheduled inspection initially and modified it somewhat, based upon our concerns of the contract monitor, for, I believe, April 25, 1978, and the inspection had to be postponed twice.

Senator KENNEDY. Would you describe what happened when FDA tried to conduct the inspection?

Dr. HENSLEY. Well, it was a rather unusual story. The inspection was scheduled for a given date, and on the night before that inspection the doctor's office was allegedly vandalized. The sofas were cut up.

Senator KENNEDY. What was cut up?

Dr. HENSLEY. The sofas, chairs; reverse swastikas were painted on the walls. It was interesting that it appeared that the certificates and diplomas had been removed from the walls before the swastikas were painted. The outlines were clearly visible where they had hung, as well as the nails. The records relating to the studies that we were going to look at, together with some other

patient records, had been dumped into a whirlpool bath, and the bath turned on overnight.

We, of course, had to postpone the investigation while the police made their reports, and did their thing. We rescheduled it for a date a couple of weeks later.

In the interim, between the first and second attempts to inspect, there was a fire that started mysteriously in the doctor's office, as well. Apparently a stack of paper towels in the middle of the floor in a backroom, next to the record room, caught fire spontaneously.

The next thing that happened was really the saddest of all, because just prior—the night before—before the rescheduled inspection, the doctor was allegedly mugged in his office and struck on the head with a steel paperweight. We have looked at police reports of that incident, and they are really undecided as to who may have done that and how it may have happened.

It is worth noting, I guess, that the only prints on the paperweight were the doctor's own prints. At any rate, we subsequently did get into the records, and were able to look at a Suprofen study, as well as a number of other studies, I think, five in total. There were virtually no records to show that the studies had ever been done. What records there were showed great discrepancies between case reports and patient charts that existed.

We subsequently interviewed patients, and it is much the same story as Doctor 31, you know, the patients said what study. No, that is not my signature on the consent form, and I think that is true for all five of the studies we looked at.

Senator KENNEDY. There were not case reports, or lab records, or many patient records, as I understand it, in that case.

Dr. HENSLEY. Yes.

Senator KENNEDY. Finally, Dr. Hensley, I would like to talk about the work of another independent monitoring firm formed by Bio-Basics' employee, who left Bio-Basics, and the study in question is that of Doctor 25, Clinical R&D Service Corp.—we invited them to appear here at the committee here today, but they declined.

This was a study on children, was it not?

Dr. HENSLEY. That is correct. It was a study of antidiarrhea drug to be conducted in children.

Senator KENNEDY. Why did FDA conduct this inspection?

Dr. HENSLEY. This was a spinoff of the Bio-Basics inspection. As we proceeded through the case, and our inspectional efforts, it became apparent that the individual involved who had left the firm and set up the second monitoring firm you were talking about seemed to be at the center of many of the problems we found, and we wondered whether or not that was just happenstance, or whether or not that was a pattern of behavior on his part. So we looked for an investigator that had worked for him, and we happened to stumble across this particular doctor during an inspection, and the results were about as you might expect.

The doctor came forward initially with a confession. He said, after we had been there a couple of days, I want to shorten this, I want to get it over with, I want to confess, and based upon his confession our inspectors prepared an affidavit, and I would like to read briefly from that, if I could.

The doctor agreed with this, but subsequently, on advice of his attorney, who happened to be his brother, he decided not to sign it, and it says: I admit I am guilty of not informing patients on investigational drugs, nor their parents, and/or guardians, that they were on investigational drugs. Neither I nor my nurses so informed the patients' guardians that they were on experimental drug study, and we did not ask for informed consent to be signed by responsible adult bringing the child.

Furthermore, my nurses signed the informed consent form on the line designated for the parent or guardian, and——

Senator KENNEDY. Before we go any further, did he confess or did he not? If he did not, I do not think there is much point——

Dr. HENSLEY. He confessed to falsification of the consent, and also to falsification of certain other documents. I think it was a phenomenon that we have seen many times before, where a doctor would confess to part of what he did, in an effort to get us to go away, and we did not go away. We persisted, and interviewed patients, and again it is the same story, and most patients appear not to exist, or, if they exist, they were not in the study.

Senator KENNEDY. Well, all in all, Doctor Hensley, we have hit on the highlights of what turns out to be 31 separate clinical investigators in different cities, different universities, different areas of private practice around the country, and I have given out this chart here which summarizes the kinds of problems that were found among these.

I do not mean to imply most of clinical investigation in the United States are like this. I do not believe that they are. I believe that most clinical investigators are honest and competent and decent people, but nonetheless, there is the nagging question of whether we are looking at the iceberg or the tip of the iceberg.

In my view, what we have heard today is a series of abuses that range from outright sloppy research to fraudulent research.

The effect of these abuses is to place the American people's health at risk. Our regulatory process depends on good data. We have heard examples that represent outright fraud or the most profound violations of medical ethics, and scientific principles imaginable. Whether it be testing a drug in humans that is not supposed to be tested in humans, or whether it is fabricating data, submitting it to FDA, upon which the decisions of the FDA are made, and which may affect whether millions of people are exposed to drugs, these abuses are unconscionable. I think FDA has done an outstanding job in investigating them. The FDA is in the process now of finalizing their regulations governing the conduct of clinical investigations with human subjects. That is why we are holding these hearings, to highlight the kinds of problems that those regulations are attempting to cover, and to urge that each pharmaceutical company, and each independent testing laboratory be required by those regulations to monitor carefully, to check patient records against case report forms, and to be responsible for monitoring and checking discrepancies between what actually happened and what is reported.

If that is not done, I do not think we will be able to cut down on this abuse, and I for one am not at all convinced that the abuse is not far more widespread than it appears at the present time.

I do not know whether there is any other additional comment we would like to make, otherwise we would express our appreciation for your appearance here, and look forward to working with you on those regulations.

Mr. GARDNER. Thank you, Senator.

Senator KENNEDY. Thanks very much.

Dr. HENSLEY. Thank you.

Senator KENNEDY. Our next panel will be Dr. Stanley Crooke, Bristol Laboratories, and Mr. George Braun, Ortho Pharmaceutical Corp.

Dr. Braun, would you care to start, please?

STATEMENTS OF STANLEY T. CROOKE, M.D., ASSOCIATE DIRECTOR OF RESEARCH AND DEVELOPMENT, BRISTOL LABORATORIES, SYRACUSE, N.Y.; AND GEORGE A. BRAUN, VICE PRESIDENT OF SCIENTIFIC AFFAIRS, ORTHO PHARMACEUTICAL CORP., RARITAN, N.J.

Mr. BRAUN. Senator Kennedy, I would request permission to read our prepared statement, if I may.

Senator KENNEDY. Sure.

Mr. BRAUN. I am George Braun, vice president of scientific affairs, Ortho Pharmaceutical Corp.

In response to a request from the subcommittee, I am providing information about clinical studies on suprofen conducted for Ortho by Bio/Basics International, an independent contract research organization.

Suprofen is a nonnarcotic, peripherally-acting analgesic agent. Following preclinical testing, suprofen appeared to be a candidate for therapy in mild to moderate pain. The decision was then made to develop suprofen for the above indication in early 1975.

Before proceeding with this statement, it is important to note that we, the drug sponsor, from the beginning and today accept the ultimate responsibility for the development of this drug. The utilization of an outside contract research firm does not change this responsibility.

In developing the plan to conduct clinical studies on this drug, Ortho identified Bio/Basics, an outside contract research organization with experience in the clinical development of analgesic compounds. Bio/Basics had access not only to recognized clinical investigators in this field of research, but also utilized recognized academic experts as a peer review group. The concept of this peer group was of particular importance to Ortho because we understood that such a group would be responsible for aiding in the design of protocols, the evaluation of data, and a review of the clinical portion of the NDA.

On September 25, 1975, Ortho contracted for Bio/Basics to conduct clinical studies to determine the safety and efficacy of suprofen. The peer group convened by Bio/Basics reviewed the preclinical and early clinical data on suprofen and issued a report indicating that the drug was safe and should be evaluated in the clinic. Bio/Basics selected investigators and initiated the studies.

During the course of the studies, Ortho, on occasion, verified that Bio/Basics personnel were monitoring the studies by visits to physi-

cians, site visits and telephone contacts. However, Ortho did not actually monitor the studies. This was a mistake.

Senator KENNEDY. Why?

Mr. BRAUN. I think the answer to that, Senator, is that we, if we are going to take responsibility for studies, must have hands on involvement.

Senator KENNEDY. Must have what?

Mr. BRAUN. Hands on involvement directly with clinical investigators.

Senator KENNEDY. And that is, I suppose, the lesson, would you not agree, you recognize that responsibility by the company?

Mr. BRAUN. Yes, sir.

Senator KENNEDY. Even if the work is done by outside contractors?

Mr. BRAUN. Yes, sir.

In October 1977, Ortho convened a meeting with Bio/Basics, members of its peer group and some of the investigators to review the progress of the studies. The objective was to get a firsthand impression from the peer group and the investigators concerning the safety and efficacy of completed studies. At this point, Ortho believed that the program was proceeding according to plan.

At about this time, FDA requested case report forms for two of the clinical investigators indicating that the request should not be construed as an adverse commentary on the investigators. In March 1978, this subcommittee conducted hearings which publicized abuses of the clinical research process.

In September 1978, the FDA inspected at Ortho the documentation of the studies conducted by the same two investigators. The true significance of these events was not fully appreciated by Ortho at the time although clearly in retrospect it should have been. However, Ortho was concurrently, in early 1978, instituting a program to establish a quality assurance group for clinical research practices which we believed to be responsive to these concerns.

The clinical studies of suprofen were essentially completed in late 1977 and in October 1978, Ortho filed its NDA. Ortho contemplated that Bio/Basics would assist it in responding to FDA technical inquiries concerning the study but Ortho would be responsible for managing the NDA through the approval process.

In November of 1978, FDA conducted an inspection at Ortho and advised that data submitted from two investigators may be worthless. In addition, the inspector revealed that, included in the Suprofen NDA were 25 patients that concomitantly received another investigational medication.

In light of these developing concerns, we recognized that substantial questions existed regarding the studies conducted by certain suprofen investigators.

In December 1978, we met with a member of the peer group to learn more about the conduct of the study, and learned that the peer group had not been utilized as originally anticipated. We then met with Bio/Basics to discuss these concerns and seek a complete review of all the documents relating to the suprofen study. They were unwilling to permit Ortho to conduct a full audit and it was several months before Ortho was finally allowed access to the documents in order to determine the validity of the clinical studies.

In view of Ortho's concerns, coupled with those of the FDA, about the validity of data, Ortho decided the responsible course of action was to withdraw the NDA, which it did on June 1, 1979.

When Ortho obtained access to the necessary Bio/Basics information, we launched an intensive audit of the clinical studies. As of this time, it appears that data from many of the studies are not usable or are usable only to a limited extent.

Senator KENNEDY. You agree then with the FDA?

Mr. BRAUN. In many cases, yes, Senator.

New studies, under our direction, have been initiated. I should note that continuing cooperation between Ortho and the FDA has enhanced the quality of that audit and our auditing procedures. They have been most helpful.

We share the view of this subcommittee and the FDA that well-conducted studies are essential to the process of drug development. Our experience has demonstrated to us the necessity for regularly conducting detailed monitoring and periodic auditing of all clinical investigations.

Senator KENNEDY. Just at this point, you think that you ought to spot-check actual case data?

Mr. BRAUN. Yes, sir.

Senator KENNEDY. Should it be required by FDA?

Mr. BRAUN. I believe that unless a company reviews source documentation and reconciles that source—by that, I mean patient records, hospital charts, reconciles that with case record forms, there is no way to be sure that that data is, in point of fact, valid. We have learned that very recently.

Senator KENNEDY. Well, if you were required to show that raw data, would you go overseas to circumvent that procedure?

Mr. BRAUN. I think there is an answer to Dr. Gardner's concern. I think we have the responsibility and the ability not to conduct clinical studies with an investigator who does not allow us access to that source documentation, and I think one way to manage that is not to conduct clinical studies with that investigator. That is one solution.

Senator KENNEDY. It certainly seems to me to be a very constructive solution, and you would certainly be the one who would feel the burden of that responsibility or obligation if that was required by the regulations. I think it is a constructive attitude and very helpful.

Mr. BRAUN. I think it is necessary.

Such procedures must be designed to provide a better understanding of the actual conduct of the study and administration of the drug, including a review of source documentation.

Thank you.

Senator KENNEDY. Dr. Crooke.

Dr. CROOKE. I would like to read a brief statement, not our testimony, but just a brief statement.

Senator KENNEDY. Let me ask this, if I could, before you begin. Do you agree with regard to the raw data?

Dr. CROOKE. Absolutely. In fact during the years since our previous visit with this subcommittee, we have initiated new auditing procedures, and have had several internal audits as well as multiple audits of specific studies.

We can discuss them in detail.

Senator KENNEDY. It is interesting that the company recognizes the importance of raw data and the Food and Drug Administration is concerned about what the attitude of the company is going to be.

The attitude of the companies in this instance is enormously constructive and positive. They recognize the importance of the availability of that data, both to insure the adequacy of the drug, and also to protect the health of the American people.

It is constructive. The Food and Drug Administration is concerned that we will lose the whole industry; that it will go overseas. I just wanted to make a comment. That is what we are trying to examine at an important point of development of these guidelines by the Food and Drug Administration.

Dr. CROOKE. I would like to read this statement. It addresses the point we have been asked to testify to: To what degree have we made progress in reviewing and auditing, and we would like to differentiate between auditing and reviewing.

Second, we would like to discuss butorphanol and all the studies in question, and such third-party monitoring as there may be.

I want to emphasize that although Bristol Laboratories formalized guidelines for good clinical practices in 1976, it has broadened the scope of its clinical practice and ethical review committee, and strengthened a number of its functions, since our presentation before this committee last year.

In addition to its previous responsibilities, the committee is responsible for reviewing all protocols, interim reports, final reports, and NDA submissions. It is responsible for providing medical-scientific consensus on all matters relating to the clinical safety of new products. It is also responsible for approval of all standard operating procedures for clinical research and assuring that all clinical research meets acceptable standards.

Very importantly, with respect to the questions before the committee, we have moved in the last year to assure compliance with corporate and Government regulations, and to insure that our submissions are accurate, we have also expanded our auditing procedures.

In fact, during the past year, several audits of our procedures, as well as audits of specific studies, have been performed.

Relative to our relationship with third-party monitoring firms, Bristol Laboratories employs consulting firms infrequently to monitor clinical research. We do so if a particular type of specialist is not on our staff and we feel we temporarily do not have the expertise to monitor a study adequately; or if our clinical staff is temporarily unable to monitor certain studies because of a period of high volume of work.

During the past 6 years, Bristol Laboratories has collaborated with consulting firms on a total of 16 studies. All of these groups were employed to study butorphanol, a potent analgesic used to relieve severe to moderate pain.

Injectable butorphanol has been the subject of 83 separate clinical studies, performed by 56 clinical investigators involving 4,439 patients. Since it was approved by the FDA in August 1978, millions of doses have been dispensed with favorable response from both physicians and patients.

Moreover, 74 clinical studies performed by 64 investigators have been conducted to demonstrate the safety and efficacy of butorphanol in oral dosage form. Bristol Laboratories believes it has sufficient data for approval of the oral new drug application even if the results of the studies performed by the three investigators cited by the FDA in its letter of October 1 were to be deleted.

We believe, as former FDA Commissioner Kennedy pointed out to this committee last year, that the scientific enterprise has for centuries developed an elaborate set of mechanisms in which trust has been assumed and has prevailed. In addition, we recognize, as he does, the need to routinely guarantee the veracity of data submitted to the FDA.

We think we have made strides toward this during the past few years.

Senator KENNEDY. Do you agree with Ortho that the final contracting work is ultimately your responsibility?

Dr. CROOKE. Certainly. I think I testified to that last year, and certainly we agree with that.

[The prepared statements of Dr. Crooke and Ortho Pharmaceutical Corp. follow:]

Statement on Behalf of
Bristol Laboratories Division of Bristol-Myers Company
Before the
Subcommittee on Health and Scientific Research of the Committee on
Human Resources of the United States Senate
on October 11, 1979

By Stanley T. Crooke, M.D., Ph.D.
Associate Director of Research
and Development

INTRODUCTION

Bristol Laboratories is a division of Bristol-Myers Company located in Syracuse, New York. We have been asked to appear to discuss our current clinical research monitoring practices, our relationships with third party monitoring companies, and to provide information relative to studies performed by specific investigators involved in clinical investigations on our analgesic, Butorphanol.

Reference is made to materials on the same general subjects presented at the hearing before this subcommittee on March 7, 1978. We will endeavor not to repeat material made a part of the record of that hearing on preclinical and clinical testing by the pharmaceutical industry, 1978.

CLINICAL RESEARCH PRACTICES AT BRISTOL LABORATORIES

We are pleased to have the opportunity to discuss our current clinical research practices. In September of 1976 Bristol Laboratories formalized guidelines for good clinical practices. These guidelines established a peer review process for all protocols, clinical operational plans, and final reports. These guidelines also established minimum monitoring standards, a standard protocol format, codified job descriptions, and minimum qualifications for each position. Furthermore procedures for handling adverse reaction reports, drugs and supplies, and for data handling

were established in these guidelines. Subsequently, the breadth of peer review was extended by addition of reviews by pharmacokineticists and toxicologists of documents requiring their review. Also, procedures for double-blind studies were altered to make it more difficult to circumvent coding, and improved methods of drug handling and inventory control were instituted.

During the year since our previous presentation to the Senate Subcommittee, we have broadened the scope of the Clinical Practices and Ethical Review Committee and strengthened a number of its functions. Specifically, in addition to previously assigned responsibilities, it is now responsible for reviewing all protocols, interim reports, final reports, and NDA submissions. It is responsible for providing a consensus medical/scientific opinion on all matters relating to the clinical safety of new products. It is responsible for approval of all standard operating procedures for clinical research, and assuring that all clinical research meets acceptable standards. It is also responsible for approving training programs of clinical research personnel.

As former Food and Drug Administration Commissioner Kennedy pointed out before this subcommittee last year, scientific enterprise has for centuries developed an elaborate set of mechanisms in which trust has prevailed.

We recognize, as he does, the need to convert a world of trust into one in which we routinely have to guarantee the veracity of data submitted to the FDA.

To assure compliance with corporate and governmental regulations, and to assure that data derived from clinical trials supported by Bristol Laboratories are accurate, we have expanded our auditing procedures.

More specifically with regard to butorphanol, which is the subject of the hearing today, when record-keeping problems were detected during monitoring visits to investigator No. 2 on studies 602-16, 603-05 and 802, full audits were performed and every patient record was scrutinized. No evidence of improper procedures was discovered. In its letter of Oct. 1, 1979, the Food and Drug Administration reported to Bristol Laboratories that it regards Study No. 58A by investigator No. 2 as questionable. Inasmuch as Study No. 58A was monitored by Biobasics, we have not audited it but will now proceed to do so. The same letter cites the work of two other investigators as also questionable. We shall perform detailed audits of these studies as well.

THIRD PARTY MONITORING FACILITIES

Bristol Laboratories employs third party monitoring facilities infrequently. During the past few years Bristol Laboratories had collaborated with consultant firms on a total of 16 studies. All of these monitoring groups were employed to study Butorphanol. Additionally, we are presently considering collaboration with a monitoring firm on two studies on antibiotic.

The decision to employ a monitoring firm may be reached for two reasons. First, if our clinical staff is temporarily inadequate to monitor certain studies because of a period of high volume of work, or if a particular type of specialist is not on our staff and we feel we temporarily do not have the expertise to monitor a study adequately, we may employ a monitoring firm. Second, occasionally a monitoring firm may be employed to provide an impartial confirmation of intramurally derived data.

The nature of the relationship between Bristol Laboratories and a monitoring firm is determined by the contract between the two parties. Thus it can vary widely. However, all contracts between Bristol Laboratories and monitoring firms must be approved by the Clinical Practices and Ethical Review Committee, the Director of Research, and the legal department of Bristol Laboratories.

Our relationship with the monitoring firm, Biobasics, encompassed a period of approximately one year between 1975 and 1976. The firm was contracted to perform studies under protocols 58 and 59. Both protocols were double blind randomized comparative trials comparing the analgetic efficacy of butorphanol administered intramuscularly to reference agents and placebo. Protocol 58 involved patients with musculoskeletal pain. Protocol 59 involved patients with post-partum episiotomy pain.

According to the terms of the contract of 1975, Biobasics was responsible for all aspects of the studies, including generation of protocols, acquisition of investigators, and

monitoring of the studies. Bristol Laboratories was responsible for generation of a randomization code, data analysis and generation of final reports.

During the conduct of the studies in question, two investigators, including Investigator No. 2 were employed for protocol 58. Three investigators, Investigator No. 1, No. 7 and No. 8, were involved in protocol 59. Study 59A performed by Investigator No. 1 was terminated by Biobasics after 15 patients were enrolled. Study 59C was terminated by Biobasics after 19 patients were entered by Investigator No. 8. A total of 137 and 162 patients were enrolled in protocols 58 and 59 respectively.

Although the monitoring of protocols 58 and 59 was the responsibility of Biobasics, Bristol Laboratories monitors visited three of the investigators including Investigators No. 2 and No. 8. During those monitoring visits by Bristol Laboratories, no discrepancies were observed in the performance of studies by Investigators No. 2 and No. 8. However, another investigator was found to have subcontracted the study to another group of investigators, and the Bristol Laboratories monitors required additional information, and additional 1572 forms before continuation of the study.

At the completion of the studies, Biobasics provided completed case reports and documentation of monitoring activities. Although additional documentation was required on some case report forms, no major deficiencies were detected.

Subsequent to the completion of studies 58 and 59, no other studies were performed in cooperation with Biobasics.

STATUS OF BUTORPHANOL

Butorphanol is a safe and effective potent analgesic. It is totally synthetic and does not depend upon opium for its manufacture. Although more potent than morphine, it has been shown in both animal and human trials to have very low addictive potential. It has narcotic antagonist properties which serve to deter abuse.

Parenteral butorphanol has been the subject of 83 separate clinical studies performed by 56 clinical investigators involving 4439 patients. It was approved by the Food and Drug Administration in August 1978 and introduced to the U.S. market in November 1978. Since then millions of doses have been dispensed with very favorable response from both physicians and patients.

As an oral medication butorphanol is several times as potent as codeine. Its safety and efficacy have been demonstrated by results obtained in 74 clinical studies performed by 64 investigators involving 3452 subjects. Bristol Laboratories filed a New Drug Application with the Food and Drug Administration in September 1978. In a letter dated October 1, 1979, the Food and Drug Administration stated that "the application is not approvable at this time... because of questions

regarding the studies conducted by (three investigators named). These studies are undergoing an audit by the Division of Scientific Investigation at this time." Bristol Laboratories believes it has sufficient data for drug approval even deleting the work of the investigators under audit.

Butorphanol, a centrally acting drug, exerts its greatest oral efficacy and duration of action when combined with a peripherally acting drug such as acetaminophen or aspirin. A New Drug Application for the butorphanol-acetaminophen combination covering the work of 36 investigators on 1120 subjects in 28 studies was filed with the Food and Drug Administration in August 1979.

Communication from the Food and Drug Administration to Bristol Laboratories within the past month is the first to indicate that as a result of audits the work of certain investigators is not regarded as acceptable at the present time. The firm has been informed by numerous butorphanol investigators other than those whose work has been cited as questionable that Food and Drug Administration personnel have audited their records over the past few years with little if any comment.

Statement on Behalf of
Ortho Pharmaceutical Corporation
Before the
Subcommittee on Human and Scientific Research of the Committee
Human Resources of the United States Senate
on October 11, 1979

In response to a request from the Subcommittee, I am providing information about clinical studies on suprofen conducted for Ortho by Bio/Basics International, an independent contract research organization.

Suprofen is a non-narcotic, peripherally-acting analgesic agent. Following preclinical testing, suprofen appeared to be a candidate for therapy in mild to moderate pain. The decision was made to develop suprofen for the above indication in early 1975.

Before proceeding with this statement it is important to note that, we the drug sponsor, from the beginning and today accept the ultimate responsibility for the development of this drug. The utilization of an outside contract research firm does not change this responsibility.

In developing the plan to conduct clinical studies on this drug, Ortho identified Bio/Basics, an outside contract research organization with experience in the clinical development of analgesic compounds. Bio/Basics had access not only to recognized clinical investigators in this field of research, but also utilized recognized academic experts as a peer review group. The concept of this peer group was of particular importance to Ortho because we understood that such a group would be responsible for aiding in the design of protocols, the evaluation of data, and a review of the clinical portion of the NDA.

On September 25, 1975 Ortho contracted for Bio/Basics to conduct clinical studies to determine the safety and efficacy of suprofen.

The peer group convened by Bio/Basics reviewed the preclinical and early clinical data on suprofen and issued a report indicating that the drug was safe and should be evaluated in the clinic. Bio/Basics selected investigators and initiated the studies.

During the course of the studies, Ortho on occasion verified that Bio/Basics personnel were monitoring the studies by visits to physicians, site visits and telephone contacts. However, Ortho did not actually monitor the studies. This was a mistake. In October 1977, Ortho convened a meeting with Bio/Basics, members of its peer group and some of the investigators to review the progress of the studies. The objective was to get a first hand impression from the peer group and the investigators concerning the safety and efficacy of completed studies. At this point, Ortho believed that the program was proceeding according to plan.

At about this time, FDA requested case report forms for two of the clinical investigators indicating that the request should not be construed as an adverse commentary on the investigators. In March 1978, this subcommittee conducted hearings which publicized abuses of the clinical research process. In September 1978, the FDA inspected at Ortho the documentation of the studies conducted by the same two investigators. The true significance of these events was not fully appreciated by Ortho at the time although clearly in retrospect it should have been. However, Ortho was concurrently in early 1978 instituting a program to establish a Quality Assurance group for clinical research practices which we believed to be responsive to these concerns.

The clinical studies of suprofen were essentially completed in late 1977 and in October 1978 Ortho filed its NDA. Ortho contemplated that Bio/Basics would assist it in responding to FDA technical inquiries concerning the study but Ortho would be responsible for managing the NDA through the approval process.

In November of 1978 FDA conducted an inspection at Ortho and advised that data submitted from two investigators may be worthless. In addition, the inspector revealed that, included in the suprofen NDA were 25 patients that concomitantly received another investigational medication.

In light of these developing concerns we recognized that substantial questions existed regarding the studies conducted by certain suprofen investigators.

In December 1978, we met with a member of the peer group to learn more about the conduct of the study and learned that the peer group had not been utilized as originally anticipated. We then met with Bio/Basics to discuss these concerns and seek a complete review of all the documents relating to the suprofen study. They were unwilling to permit Ortho to conduct a full audit and it was several months before Ortho was finally allowed access to the documents in order to determine the validity of the clinical studies.

In view of Ortho's concerns, coupled with those of the FDA, about the validity of data Ortho decided the responsible course of action was to withdraw the NDA, which it did on June 1, 1979.

When Ortho obtained access to the necessary Bio/Basics information we launched an intensive audit of the clinical studies. As of this time, it appears that data from many of the studies are not usable or are usable only to a limited extent. New studies, under our direction, have been initiated. I should note that continuing cooperation between Ortho and the FDA has enhanced the quality of that audit and our auditing procedures.

We share the view of this subcommittee and the FDA that well conducted studies are essential to the process of drug development. Our experience has demonstrated to us the necessity for regularly conducting detailed monitoring and periodic auditing of all clinical investigations. Such procedures must be designed to provide a broad understanding of the actual conduct of the study and administration of the drug, including a review of source documentation.

Senator KENNEDY. Thank you very much. It has been helpful testimony, and we appreciate it.

Our next witness is Dr. Stephen DeFelice, President of Bio-Basics International.

STATEMENT OF STEPHEN DeFELICE, M.D., PRESIDENT, BIO-BASICS INTERNATIONAL CORP., NEW YORK, N.Y., ACCOMPANIED BY JAMES R. PHELPS, ESQUIRE

Dr. DeFELICE. Senator, I am not going to read by prepared statement. A lot of it has been said today.

Senator KENNEDY. You want your statement in the record?

Dr. DeFELICE. You have it, and I have a supplemental one after having read Ortho's statement.

Mr. PHELPS. We would like to submit that, too.

Senator KENNEDY. They will be included in the record in their entirety at the conclusion of your testimony.

Dr. DeFELICE. Bio-Basics hasn't been accused today of any wrongdoing; why are we here?

Senator KENNEDY. We make no accusations. They report the results of their various investigations which have affected your company. This is the result of their investigations. They have testified to the nature of their particular findings, and on an issue which has enormous importance and consequence to the basic safety and health of the American people.

You are an independent contractor, and you are welcome to make whatever comments you wish on those issues and those problems.

We are not scientists, but the Food and Drug Administration has an important responsibility. It is charged by the Congress of the United States to provide for the safety and efficacy of various drugs which are going to be consumed today and they have made those findings on questions which reach the whole regulatory process.

We want to give you an opportunity to testify. There may or may not be additional actions which will be taken.

We want to give you every opportunity to make whatever kind of comment you wish on that. We are the forum in which they make those charges which are enormously important and significant in terms of the public health of the American people, the elderly people, the children, the men, and women of our society.

They are in the process of developing finally the regulations dealing with the monitoring that they are going to have in order to make sure that this process is going to function and work in the way that it should so that the scientific process in which the Food and Drug Administration is going to make this decision is going to be sound.

They are going to develop those regulations. This committee started in the areas of finding this type of problem 2 to 3 years ago. Those regulations have been up for consideration for over 2 years.

I, quite frankly, feel they should move a good deal faster, based upon the results of the various hearings.

Now I am concerned about the potential change in those potential regulations, in not being able to examine the raw data. We hear from companies who feel they should provide it, and it ought

to be provided to protect the safety and health of the American people. If the Food and Drug Administration has made statements, and you have responses, you ought to be able to have whatever opportunity necessary in the same forum in which they have made those findings public, to be able to express a view about it.

Dr. DEFELICE. How could I respond if I haven't been told? I haven't been told.

Senator KENNEDY. You don't know?

Dr. DEFELICE. I haven't been told. I have heard things and there are hints. I have been told partial things, but I requested information from the Food and Drug Administration and I requested information from your staff.

I requested specific questions that would be asked of me at this meeting. Why am I here?

You congratulated Dr. Hensley for a job well done, which means that what he found out was right. I disagree. I have not found out what is specifically wrong. I have not been able to rebut anything for a year. I have not been able to rebut anything.

We are the leading monitoring company. We were checking raw data before this concept became popular. You put us out of business by these indirect accusations.

Next week, I will have to tell my staff, for reasons that I don't know, for reasons brought up in public, Bio-Basics will close shop. I would like to hear some specifics.

What are you talking about?

Senator KENNEDY. Are there problems, or aren't there?

Dr. DEFELICE. Yes, the problems which relate to understanding clinical research and clinical drug development. Understanding this, you don't hire people and train them for 6 weeks and send them in the field to look at the problem of oral analgesics in the midseventies. It was a new area. Very few investigators.

Dr. Hensley rightly picked up changes on protocols, but this is why you monitor. You monitor to find problems, and you correct them. Whether you agree or disagree is a matter of debate.

I wish I was told what was wrong so I could rebut it.

Senator KENNEDY. You were given the names of the doctors?

Dr. DEFELICE. No fooling? Big deal. Good deal. I just found out the details that Dr. No. 3 gave. I called him yesterday for the first time. The next before the second visit, when his office was broken into—

Senator KENNEDY. We avoid mentioning names. We have given your lawyers the names of the doctor and the allegations and charges.

Dr. DEFELICE. Dr. No. 3 to us is a good investigator—OK? We like him. We think he did a good job. He was hospitalized. He lost his sight, partial vision in one of his eyes.

He has been accused of being struck on the head with a metal object, and put in the hospital under intensive care in order to hide some data. I don't think that is true. It may be; it may not be.

The police are not sure.

Senator KENNEDY. There were three aspects of it. One is that the night before the investigation, his office was burglarized, and all of his records, medical records, put into a whirlpool, and virtually destroyed. That was one aspect.

On the second investigation, there was a fire. Whatever other records there were, were destroyed; and, third, there was the instance of the mugging.

Dr. DeFELICE. But they didn't mention the loss of his sight, or that he was hospitalized:

Senator KENNEDY. The point that the Food and Drug Administration alleged on that is that the information that they were able to draw on the basis of their investigation and talking to patients, show it was basically fraudulent.

You believe he was a good investigator. Those were the circumstances which the Food and Drug Administration has indicated, the series of circumstances in which the information or the records were completely destroyed; and the patients denied even being included.

Dr. DeFELICE. Senator, my Gosh, the guy is in the hospital; he has lost his sight; he can't practice medicine. He can't do surgery full time. Maybe yes, or maybe no.

First of all, I should have been told about it before I came. Also, we are kind of hasty in our judgments. It has been indicated that Dr. No. 3 called patients and frightened them. I am getting at a whole method in which Bio-Basics was inspected.

There wasn't a lawyer in our office for a long time. The Food and Drug Administration was in our office everyday. I told Dr. Hensley to do it, and do it well, but the rules of the game are that I am not supposed to know the results, just the investigator.

Here we are, a good house, straight, good guys and gals. We instituted monitoring and raw data examination before other people.

Senator KENNEDY. Why didn't they find out these things?

Dr. DeFELICE. The trick—I am not sure what they found, No. 1, except what I hear through the grapevine, and I disagreed with what I heard.

Senator KENNEDY. Here we had Ortho, who testified here that they had audited one of the drugs being considered, in which you are doing the tests, where they agree with the Food and Drug Administration.

Dr. DeFELICE. I am saying that I disagree.

Senator KENNEDY. It is their drug?

Dr. DeFELICE. They didn't agree.

Senator KENNEDY. I will ask the reporter to read back exactly what they said. They are still here. They said in some of the instances.

Dr. DeFELICE. In some of the instances, OK, they may agree. We are not inept. We are experts in clinical research. We have not been asked. This is what is bothering us.

In the midseventies we did not go to raw data. We were the first subsequently to go to the programs we talked about.

If a doctor wants to confabulate, he can, and create patients. We had four layers of monitoring.

Senator KENNEDY. Did you provide for Ortho's access to the material?

Dr. DeFELICE. Let me tell you about the statement of Ortho, about which I was very unhappy last night.

Senator KENNEDY. You are unhappy about the statement?

Dr. DEFELICE. Yes. And I have a supplement to counter that.

We were in constant communication with Ortho throughout this program. When they heard of our inspection, the FDA inspection, they came to us and asked for certain records which are confidential, for instance, monitoring records, et cetera.

I said it would be fine as long as you tell me what you are going to do with respect to settling this issue. In the meantime, the Food and Drug Administration is telling our chief sponsor that we are being inspected, and I cannot rebut it. I don't know what the accusations are, so we haven't any business on account of leaks from the Government.

We say OK, we want to resolve this issue; open the files; et cetera. We would not open our files until we had this commitment from Ortho. They came subsequent to that and made a commitment to speedily bring this to a conclusion, to bring this speedily to a conclusion, and we did open up. We thought we were going to cooperate, and we haven't heard too much from them since.

I don't know the results of their audit, or the Food and Drug Administration's audit, and here I am being accused today—

Senator KENNEDY. What are the results of your own audit?

The nature of our inquiry has varied as it did during the course of the hearing today, not dissimilar from hearings that we had 2 years ago, which had been targeted on sloppiness, on fraud, on misrepresentation by various doctors. And that was what we were interested in before; but we communicated to your company and your attorney, indicating that that is exactly what we are interested in this time.

Dr. DEFELICE. Does sloppiness make you not competent?

Senator KENNEDY. Sloppiness and fraud.

Dr. DEFELICE. Be careful, because I heard sloppiness mentioned equally with fraud. There is a great difference.

Senator KENNEDY. What does your monitoring show?

Dr. DEFELICE. Our monitoring shows that the investigation of Suprafen was conducted in a way that shows that it is a safe and effective analgesic. We stand behind it. We did not go to raw data as Dr. Hensley did, because it requires three or four people.

Senator KENNEDY. Have you done an audit of your own work?

Dr. DEFELICE. Yes.

Senator KENNEDY. And on the raw materials?

Dr. DEFELICE. Sometimes.

Senator KENNEDY. Will you provide this for the Committee?

Dr. DEFELICE. I will, subsequent to this. It takes awhile to put it together.

Senator KENNEDY. Do you mean a long time?

Dr. DEFELICE. It takes some time to put it together.

Senator KENNEDY. Have you got it?

Dr. DEFELICE. We have got some. Let me finish.

Senator KENNEDY. How much have you done in terms of the examination of raw data?

Dr. DEFELICE. I would have to check. We have made spot checks.

Senator KENNEDY. You have to check?

Dr. DEFELICE. If Dr. No. 3's records existed—they don't exist, No. 1.

Senator KENNEDY. You know his work is good?

Dr. DeFELICE. Some records we can't get to because of this investigation. We have to make a judgment that says, for example, you take one of these investigators—take Dr. No. 3 again. If there are discrepancies on patient records, that doesn't mean the patient didn't exist. That doesn't mean the patient didn't receive the drug. That doesn't mean his pain didn't go away.

It could be an error. The patient could not have created it, but we have found, for example, on certain data information, that there were discrepancies in case report forms, and the clinical case report forms, but those discrepancies do not invalidate the study.

In other words, there might be a fracture instead of a sprain—things of that nature. Substantial changes that would invalidate the study, we have not found anything like that to date.

We weren't hiding anything. Dr. Hensley was insisting that he look at our files. The problem with Ortho had nothing to do with any desire to be secretive. At the time Ortho requested access to our secret files, the Food and Drug Administration had already been given copies of these documents, so we cannot be accused of trying to withhold data from anyone.

Senator KENNEDY. Well, the Food and Drug Administration has looked at nine of your studies, and found eight of them to be deficient, virtually worthless.

Dr. DeFELICE. Right.

Senator KENNEDY. You have indicated to us that you have got the most up-to-date monitoring system, as you say.

Dr. DeFELICE. We look at raw data now.

Senator KENNEDY. What I am asking is, in those areas where they have found that it has been virtually worthless, what does your examination, monitoring of raw data, show? Summarize that.

Second, will you provide that analysis for this Committee, so that we can examine it?

Dr. DeFELICE. What was the second point, Senator?

Senator KENNEDY. Will you provide that information, your own studies of those particular studies, and make them available to the committee so we can examine them, sir?

Mr. PHELPS. My name is James R. Phelps. I am here representing Dr. DeFelice.

We can do that best if we get the criticism. We are operating in a blind. Sloppiness is a very broad word that does not convey a lot of meaning.

If we are told what the criticisms are, it would help us. We hear you are operating from raw investigational files, that so far as we can tell have not been screened within the agency itself.

If you can tell us exactly, that would protect the confidentiality. If we could know what is being charged, we could have the ability to provide the facts which underpin the assertion of sloppiness.

It is very important.

Dr. DeFELICE. The thing that Ortho seems to have known, they agree with the Food and Drug Administration in some of the areas in terms of the deficiencies that have been found.

Mr. PHELPS. They have not told us or quantified it.

Dr. DeFELICE. Let me give you some examples.

Senator KENNEDY. In the particular areas supplied by the Food and Drug Administration, did you look at those?

Dr. DEFELICE. They didn't tell us.

Senator KENNEDY. Have you done independent monitoring?

Dr. DEFELICE. Yes. We looked at what were the major objections of the Food and Drug Administration. I can't define sloppiness.

Senator KENNEDY. You provided information to the Food and Drug Administration?

Dr. DEFELICE. Our raw report forms.

Senator KENNEDY. You know what information the Food and Drug Administration has, because you provided the information to them.

Mr. PHELPS. No.

Senator KENNEDY. You don't know what you gave them?

Dr. DEFELICE. No; they don't make the judgment from what we gave them.

Senator KENNEDY. That is the basis?

Dr. DEFELICE. That is the focal document.

Senator KENNEDY. That is the focal document.

Dr. DEFELICE. If you want to take an example which disturbed the Food and Drug Administration more than other ones—Dr. Hensley is here. Maybe he can verify this, No. 6?

Senator KENNEDY. I don't think he testified on No. 6.

Dr. DEFELICE. No. 6 was a big issue.

Senator KENNEDY. What have you got there? Particulars on No. 6?

Dr. DEFELICE. No, one aspect of what I know of certain aspects of an inspection, which I considered Dr. Hensley to be justified in.

Mr. PHELPS. I think you should understand how we get our information.

Senator KENNEDY. You know all about No. 6?

Mr. PHELPS. We don't know all about it.

Senator KENNEDY. But you have some information on No. 6 that you want to get into the record? It wasn't mentioned here.

Mr. PHELPS. It is critical that you understand that we are operating with rumors. We are hearing what a Food and Drug Administration inspector said to X or to Y, and prompted really by a concern that that would be the topic of this hearing, we went out and tried to talk to people.

We don't know what facts the Food and Drug Administration is using as a basis.

Senator KENNEDY. We are not interested in who has been talking to whom, but what the facts are in a particular study. If you have done the monitoring on the study, and you have made your conclusions, and the Food and Drug Administration has some, then you will provide your own analysis to us.

We are not trying to second-guess and get hearsay. We would want to know the nature of the study.

Mr. PHELPS. We cannot answer criticisms that we don't know what they are.

Senator KENNEDY. You stand behind each and every one in terms of your monitoring?

Mr. PHELPS. Yes.

Dr. DEFELICE. Yes.

Senator KENNEDY. In terms of monitoring your own work?

Dr. DEFELICE. Yes.

Senator KENNEDY. And you stand behind all of the work you have done in each part of that, and the parts that have been done for you?

Dr. DEFELICE. Yes. Do you mean do we stand behind the results? Yes, of the Suprafen program.

Senator KENNEDY. That you have done and that has been done for you by the doctors who have done the research?

Dr. DEFELICE. Yes.

Senator KENNEDY. We heard the two companies very creditably say that they take complete responsibility all the way through, and they make constructive suggestions on how best those regulations could be drafted.

You, as I understand here, state that you have examined the work that has been done by your company operations, and that which has been done for you, and you stand behind that?

Dr. DEFELICE. We have no reason not to stand behind it at this point. This is the problem.

Senator KENNEDY. You have monitored it, and you stand behind it?

Dr. DEFELICE. Right.

Senator KENNEDY. And the Food and Drug Administration does not agree with this?

Dr. DEFELICE. Right.

Senator KENNEDY. Neither does one of the companies for which you work for?

Dr. DEFELICE. I am not so sure. You can ask them. Not according to their statement. It said, "some data." How do you quantify "some"?

Senator KENNEDY. When they try to develop and find a system in which the scientific information is going to be scientific and professional, that is the question.

Mr. PHELPS. Senator, I hope you understand what "some data" could mean. It could mean that one or two patients in a large study were found to be disqualified for use for some reason or other, so the expression "some data", until it is quantified, is impossible to respond to.

Senator KENNEDY. Well, just looking through the record of a transcript with Ortho on these particular points here, here is the staff interview with Ortho.

Question. Do you have a breakdown of the 24, talking about the 24 studies, and how many appear to be valid?

Mr. BRAUN. You also must remember my statement may not correspond with what the FDA's judgment is on an investigator, but I would hope, and I underscore the word hope, that we would be able to identify three or four investigators that we feel probably are defensible.

The way I read that is 3 or 4 out of 24.

Mr. PHELPS. That is the first time we have heard that.

Senator KENNEDY. You have got the monitoring system in your own shop. It is either so or not so. We want to find out if you have your own monitoring system which would show this up.

The testimony you are giving as far as your monitoring of your own programs, none of this has shown up?

Dr. DEFELICE. A more important issue for the Senate, since we are talking about guidelines, would be the mechanism in resolution of the problems of this nature.

Maybe Dr. Hensley is right. I don't know. We don't know either.

What I am saying is that you cannot let this thing drag on and be settled in open forum.

Mr. PHELPS. You mentioned, did you find any problems?

Dr. DeFelice said the very purpose of monitoring is to find problems.

Dr. DEFELICE. That is what we have been accused of—finding problems. We are the first large monitoring house in the United States. This was to produce clean data. This was the concept.

[The prepared statement statement of Dr. DeFelice follows:]

STATEMENT OF STEPHEN L. DEFELICE, M.D., PRESIDENT, BIO/BASICS
INTERNATIONAL, INC.

My name is Stephen L. DeFelice. I am president of Bio/Basics International, Inc.

I am a physician and I have trained as a fellow in endocrinology and clinical pharmacology. I was chief of clinical pharmacology at the Walter Reed Army Institute of Research. There I was responsible for the clinical development of drugs for the Federal Government in areas such as the treatment of malaria and prevention of injuries due to radiation by the hydrogen bomb. After that, I was medical director at Pfizer and was involved in the clinical development of many different types of compounds for a variety of diseases.

In addition to my position at Bio/Basics, I am presently chairman of the Foundation for Innovation in Medicine. The purpose of the Foundation is to encourage the removal of barriers to innovation. (I created this Foundation as a result of my discovery of a natural substance which promises to have great potential in the treatment of cardiovascular disease as well as muscular dystrophy.)

Bio/Basics was created by me to perform two functions: (1) Objectively plan NDA development programs, and (2) Conduct and monitor clinical trials. Bio/Basics has been the leader in this field.

Bio/Basics has been advised that the purpose of this hearing is to consider FDA's proposed regulations related to clinical testing. In the past, Bio/Basics has responded to FDA

and suggested ways to tighten the monitoring of clinical research. Our comments were based upon our experience in monitoring numerous clinical investigations--not theoretical considerations. As a part of the evolution in the profession of conducting and monitoring clinical investigations, Bio/Basics has refined and adopted procedures which are wiser and more pertinent, we believe, than those set forth in the proposed regulations. For example, FDA proposes that a twelve month interval between monitoring visits is acceptable. It is not. Through experience we have learned that frequent monitoring, particularly in the early phases of clinical research, is essential. Only in this way can sloppiness and inconsistencies be detected and attempts made to correct them. This is the purpose of monitoring. If clinical research were errorless, there would be no need for monitoring to detect errors, sloppiness and inconsistencies.

We are attaching for the record a copy of our procedures and we commend them to this Committee and to the FDA. Our procedures, we believe, ensure accurate on-site monitoring of both clinical case reports and source records, as well as an orderly flow of documents from clinical investigators through the monitor to the drug sponsor. In addition, the procedures devote considerable detail to ensuring that any changes on the case report forms are properly made and verifiable.

Because we have been directed to limit our remarks to no more than ten minutes, I will not attempt to delineate all of the efforts Bio/Basics has taken to improve its monitoring

program, nor will I attempt to dissect FDA's regulations, point-by-point.

We have been advised by Subcommittee staff that this hearing will also focus upon the activities of a number of clinical investigators, including some who participated in studies that Bio/Basics monitored.

I should point out initially that these studies were all begun and completed prior to publication of FDA's proposed regulations in September 1977. Thus, the extent to which the proposed regulations have changed clinical investigations and monitoring is in no way reflected by an examination of these studies.

I should also point out that Bio/Basics has spoken on many occasions to the FDA and Subcommittee staff in an attempt to ascertain the specific scope of inquiry regarding these clinical investigators. We have been unable to obtain such information. Thus, given the voluminous nature of the documents involved in clinical studies, I may not be prepared to answer every question which the Subcommittee asks.

We have been told that one problem seems to be verifying information on the case report form (CRF) with the patient records. If that is so, then the Subcommittee should understand that at the time these two studies were conducted, it was not a practice to review source records. In fact, many investigators would not provide access to these records even if asked. Because of certain reports about falsified data, in

other studies not involving Bio/Basics, some of which this Committee was responsible for bringing to public light, procedures have been changed to deal with this infrequent eventuality. Thus, Bio/Basics, as a regular part of its monitoring efforts, began checking source records, before the monitoring guidelines were proposed, to make sure that they are compatible with the case report forms submitted by the investigators. At the time these two studies were conducted, we and no one else we know examined patient records. This meant we would not detect an investigator who "created" patients. Now we can.

As we have attempted to prepare for this hearing, we have learned that much could be done to improve the way FDA deals with investigators. These people are scientists, unaccustomed to dealing with government inspectors. The process of interrogation and examination has been reported to us to be frequently unproductive and intimidating. The very fact of the investigation is made public through FDA and that of course is damaging. We have learned that in some instances patients have been called and told their doctor was being investigated. With greater forethought, the investigations can be run fairly and without unnecessary trauma.

Clinical researchers are not lawyers. I am quite convinced that good clinical investigators doing good work will continue to be unfairly judged by FDA inspectors. I would propose, therefore, that a method of counselling be established to help the investigators deal with FDA inspectors.

A second point that has been raised is the alleged sloppiness and inconsistency of certain data in some of our clinical trials. I categorically and forthrightly challenge this accusation. The statement is based on a profound lack of understanding by FDA inspectors of the nature of clinical research and the context in which it was conducted. Bio/Basics has been living under the cloud of this inspection for over a year now without a chance of rebuttal.

During the mid-1970s, expertise in oral analgesic clinical research was far behind those of other specialties. It was a relatively new field without an abundance of clinical investigators. In fact, even with known analgesics, such as aspirin, a high percentage of investigators failed to show differences between the active analgesic and placebo. It became important, therefore, to determine whether an investigator could differentiate active drug from placebo. In the Suprofen program, therefore, a positive control--aspirin--was added. It was critical to determine whether an investigator could differentiate placebo from a known analgesic. If he could not, then he could not be expected to detect the difference between Suprofen or Butorphanol and placebo. This was simply a type of quality control. If we found that the investigator could not differentiate between aspirin and placebo, then we would look for the cause. It could be sloppiness, inconsistencies or errors. Identifying these problems is the purpose of monitoring. We looked for the cause of errors and then tried to correct them. We find ourselves now,

in effect, being accused of doing good monitoring. We are probably the most intensively inspected third party in the history of clinical research. We invited FDA to do an open audit even before the inspection began. We are disappointed that FDA appears to lack the expertise to understand and evaluate good monitoring practices.

In the final analysis, Suprofen is a safe and effective analgesic. Indeed, FDA has commented that the "pain" ratings were the most consistent, or non-corrected items of the case report form. The question of safety, to our knowledge, has not been raised. Bio/Basics has done its job well. I truly wonder how we will finally resolve this dilemma.

Differences of opinion will occur in the future. We need a mechanism for quick resolution to bring fairness to the system, both for the investigator and the patient. After all, the proposed monitoring guidelines may add another significant roadblock in bringing new therapies to patients. We do not need more drug lag.

And finally, with respect to my colleagues at Ortho, I would like to make some general comments. They have, like Bio/Basics' clinical investigators, been intimidated by this entire process. During the Suprofen clinical program, we had open communications with them. Problems of communications occurred after the clinical studies that we are discussing today were completed. Ortho is a reputable company, and I would urge them to

join us to bring to a close this unfortunate investigation of Suprofen.

We assess the results of the FDA monitoring program as mixed. There has been a great awareness developed concerning the need for record-keeping and procedures for catching the rare corrupt investigator. These are helpful. On the other hand, the investigative process, once launched, seems interminable; clinical investigators and others are as a result caught in a battle with rumors that they cannot answer. This is unfair.

The people of this country deserve good clinical work and they can have it. The process begun by this Subcommittee has helped move us to this goal. Care must be taken, however, to make the process fair. Careful and correct investigations, speedily resolved, must be achieved.

7

Senator KENNEDY. OK. I will ask the staff to meet with your attorney, so there will be an opportunity to review those particular studies which you have done, and we will include those that you think will be helpful in the record.

Mr. PHELPS. We would appreciate that, Senator.

Senator KENNEDY. OK.

Finally, we commenced hearings in the area of animal testing with our oversight of clinical monitoring. That was about 2½ or 3 years ago, and the development and the expansion of these problems needed biomonitoring of the program.

Our committee has reviewed that, and we are going to continue to review it.

As a result of those initial hearings, we were able to get additional resources, additional appropriations for the Food and Drug Administration, and more intensive monitoring has taken place over the period of the last 2 to 3 years.

These cases which we have heard over the course of the hearing this morning have been developed over the period of the last 2 years. Some of them can be traced back in terms of the doctors themselves.

There have been people who have been active in that program of drug testing, going back for a number of years, but nonetheless, the kinds of conclusions drawn by the Food and Drug Administration have been recent.

We are not scientists here, but they have made, I think, some very important statements, and have drawn some important conclusions, which reach the heart of the process of the Food and Drug Administration's responsibility to provide for the safety and the health of the American people, and this is an extremely important matter.

As they are developing these regulations in this area, it is imperative, I believe, that they be developed in such a way that the Food and Drug Administration is going to do the best in terms of getting scientific information so they can make judgments to protect the American people.

We have heard today about a so-called physician without a license practicing medicine and testing drugs; about a physician getting a license in one State and getting reciprocity in another State, and still practicing; we have heard of other physicians totally fabricating the data, and that person is practicing today in the U.S. Navy. We have heard of a famous case of changing X-rays. We have heard of others testing drugs, in patients, when they are forbidden to do so.

It puts patients at risk, receiving drugs approved on fraudulent data.

No one is accusing Bio-Basics of anything. The FDA has looked into nine of your studies, and found eight to be deficient. The primary companies turned over to you the responsibility to monitor the data, how that monitoring data has been broken down, and the integrity of the scientific data, is at the heart of the regulatory problem.

We are concerned about the American people, and tests on children without informed consent; we are concerned about people practicing medicine without a license; we are concerned about people who practice without regard to Food and Drug Administration regulations, and produce fraudulent and deficient data that places all of us at risk.

These are issues of very considerable importance to the American people and to the Congress, and to this committee. We are going to continue to monitor these issues closely and to work with the Food and Drug Administration, and with the various companies as well.

If there is no further comment, the Committee stands in recess.

[Whereupon, at 12:15 p.m. the subcommittee stood in recess, subject to the call of the Chair.]

The first of these is the fact that the
the second is the fact that the
the third is the fact that the

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